



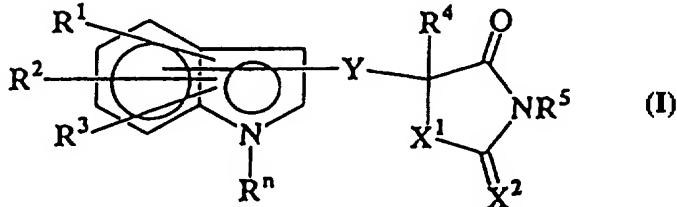
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 417/06, 413/06, 417/14, A61K 31/425, 31/42</b>		A1	(11) International Publication Number: <b>WO 96/26207</b>
(21) International Application Number: <b>PCT/JP96/00403</b>			(12) International Filing Date: <b>22 February 1996 (22.02.96)</b>
(30) Priority Data: 7/34963 23 February 1995 (23.02.95) JP 7/336391 25 December 1995 (25.12.95) JP			
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Published With international search report.			

## (54) Title: THIAZOLIDINE AND OXAZOLIDINE INDOLES WITH HYPOGLYCEMIC ACTIVITY

## (57) Abstract

An indole type thiazolidine compound of formula (I) and its salt, wherein X<sup>1</sup> is S or O; X<sup>2</sup> is S, O or NH; Y is CR<sup>6</sup>R<sup>7</sup> (R<sup>6</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>7</sub> alkyl group); R<sup>1</sup> is a substituent at the 2-, 3-, 4-, 5-, 6- or 7- position of an indole ring and is a C<sub>1</sub>-C<sub>10</sub> alkyl group, -W<sub>k</sub>-V<sub>l</sub>-Z (Z is a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, a C<sub>6</sub>-C<sub>14</sub> aromatic group, a C<sub>1</sub>-C<sub>12</sub> heterocyclic aromatic group, a C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic group, etc., V is O, S, etc., W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups, and each of k and l is 0 or 1), -V-W-Z (V, W and Z are as defined above), -W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different), or R<sup>1</sup> may be a hydrogen atom when Y is bonded to the 4-, 5-, 6- or 7-position of an indole ring; each of R<sup>2</sup> and R<sup>3</sup> is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring, and is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, or the like; R<sup>4</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>7</sub> alkyl group; R<sup>5</sup> is a hydrogen atom or a carboxymethyl group; and R<sup>n</sup> is a substituent at the 1-position of an indole ring, and is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, an alkylsulfonyl group, an arylsulfonyl group, or the like.



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DESCRIPTION

THIAZOLIDINE AND OXAZOLIDINE INDOLES WITH HYPOGLYCEMIC ACTIVITY

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TECHNICAL FIELD

The present invention relates to novel indole type thiazolidines having a hypoglycemic effect and aldose-reductase inhibitory activities, which are useful in medical and veterinary fields, particularly useful for 10 preventing or treating diabetes mellitus and diabetic complications.

BACKGROUND TECHNIQUE

Heretofore, various sulfonylurea derivatives and biguanide derivatives have been widely used as oral 15 hypoglycemic agents for lowering blood sugar levels. However, these agents had disadvantages of causing serious hypoglycemic coma and lactic acidosis revelation, and therefore every possible care must have been taken for practical use. "Chem. Pharm. Bull., vol. 30, p. 3563 20 (1982)", "J. Med. Chem., vol. 32, p. 421 (1989)", "J. Med. Chem., vol. 34, p. 318 (1991)", "J. Med. Chem., vol. 33, p. 1418 (1990)", Japanese Unexamined Patent Publication No. 64586/1980, and European Laid Open Patent Publications No. 177353, No. 283035, No. 283036, No. 25 332331, and No. 332332 disclose various thiazolidindiones which achieve a hypoglycemic effect, and these are particularly useful for treating Type II diabetes and are

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noted as agents for hardly causing such hypoglycemic symptoms as caused by the above-mentioned oral hypoglycemic agents. However, although these compounds have a function of effectively lowering a blood sugar 5 level, it is not proved that these compounds have effects for reducing or preventing various chronic symptoms caused by diabetes, such as diabetic nephropathy, diabetic cataract, diabetic retinopathy, diabetic neuropathy and the like.

10 Further, some of a series of indole derivatives having a thiazolidine ring or an oxazolidine ring as a partial structure, are known. For example, there is reported in Bioorg. Med. Chem. Lett., vol. 2(7), P705 (1992) that a series of 3-((4-oxo-2-thioxo-5- 15 thiazolidinylidene)methyl)indole derivatives have cyclooxygenase and 5-lipoxygenase inhibitory activities. Arch. Pharm. (Weinheim),, vol. 304(7), P523 (1971) and European Patent No. 343643 disclose that a series of 2-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole 20 derivatives have anti-inflammatory and anti-allergy activities. Japanese Examined Patent Publication No. 56175/1986 and European Laid Open Patent Publication No. 47109 disclose that a series of 3-((N-carboxymethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole 25 derivatives have aldose-reductase inhibitory activities. Indian Drugs, vol. 22(10), P519 (1985) and J. Chem. Soc. Pak., vol. 4(1), P43 (1982) discloses a series of 3-((4-

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oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have CNS activities. Japanese Unexamined Patent Publication No. 96941/1980 discloses that a series of 3-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives are useful as a photographic material of silver halide. Anal. Lett., vol. 17(A13), P1447 (1984) discloses that 3-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole is useful as a spectroscopic analytical reagent. J. Med. Chem., vol 21 10 (1), P82 (1977) discloses that a series of 3-(4-oxo-2-thioxo-5-thiazolidinylmethyl)indole derivatives have anti-bacterial activities. J. Med. Chem., vol. 10(5), P852 (1967) discloses that a series of 3-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have decarboxylase inhibitory activities. However, it is not known at all that these compounds have a hypoglycemic effect.

Belgian Laid Open Patent Publication No. 889758 discloses that a compound having 2,4-dioxo-5-oxazolidinyl 20 directly bonded with an indole ring as a hypoglycemic effect on rats. However, these compounds are not actually synthesized, and their effects are not clear. Also, US Patent No. 4,738,972 and PCT Publication No. 8607056 disclose that a compound having 2,4-dioxo-5-thiazolidinyl directly bonded to the 5-position of an 25 indoline ring has a hypoglycemic effect on ob/ob mice. However, these compounds are not actually synthesized and

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their effects are not clear. European Laid Open Patent Publication No. 587377 discloses N-substituted 2- or 3-indolylmethylene-2-thioxo-4-thiazolidinone has a hypoglycemic effect on yellow obese diabetes mellitus 5 mice, but its effect is not satisfactory.

On the other hand, aldose reductase (AR) is known to be an enzyme for reducing aldoses such as glucose and galactose to polyols such as sorbitol and galactitol in a living body. It is also known that accumulation of the 10 polyols thus produced by the enzyme in organs induces or exacerbates various diabetic complications such as diabetic retinopathy, diabetic neuropathy and diabetic nephropathy, and therefore an inhibitor against this 15 enzyme is useful as an agent for treating these diabetic complications.

Under these circumstances, the present inventors have synthesized various thiazolidines which are not disclosed in the above-mentioned literatures, and have studied their properties. As this result, the present inventors 20 have found compounds having excellent hypoglycemic effects and aldose-reductase inhibitory activities which were not exhibited by the above-mentioned known compounds. Thus, the present invention provides indole 25 type thiazolidines capable of preventing or treating diabetes mellitus and diabetic complications.

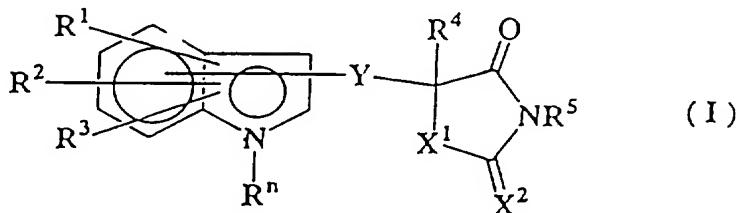
#### DISCLOSURE OF THE INVENTION

The novel indole type thiazolidine derivatives of the

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present invention are indole type thiazolidines of the following formula (I) and their salts:

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wherein  $X^1$  is S or O;

$X^2$  is S, O or NH;

Y is  $CR^6R^7$  ( $R^6$  is a hydrogen atom, a  $C_1-C_7$  alkyl group or a  $C_3-C_7$  cycloalkyl group, and  $R^7$  is a hydrogen atom, a  $C_1-C_7$  alkyl group or a  $C_3-C_7$  cycloalkyl group, or forms a bond together with  $R^4$ );

$R^1$  is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring, examples of which include a  $C_1-C_{10}$  alkyl group, a  $C_2-C_{10}$  alkenyl group, a  $C_2-C_{10}$  alkynyl group, a  $C_1-C_{10}$  alkoxy group, a  $C_2-C_{10}$  alkenyloxy group, a  $C_1-C_{10}$  alkylthio group, a  $C_1-C_{10}$  monoalkylamino group or a di- $C_1-C_{10}$  alkylamino group (each of said  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{10}$  alkynyl,  $C_1-C_{10}$  alkoxy,  $C_2-C_{10}$  alkenyloxy,  $C_1-C_{10}$  alkylthio,  $C_1-C_{10}$  monoalkylamino and di- $C_1-C_{10}$  alkylamino groups may be substituted with a hydroxyl group or a  $C_1-C_7$  alkyl group), or

$-W_k-V_\ell-Z$  (Z is a  $C_3-C_{10}$  cycloalkyl group, a  $C_3-C_7$  cycloalkenyl group, a  $C_6-C_{14}$  aromatic group, a  $C_1-C_{12}$  heterocyclic aromatic group (said heterocyclic aromatic group may contain at most 5 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and

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a nitrogen atom as constituents for the heterocyclic ring), or a C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic group (said heterocycloaliphatic group may contain at most 3 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring) (each of said C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, C<sub>6</sub>-C<sub>14</sub> aromatic, C<sub>1</sub>-C<sub>12</sub> heterocyclic aromatic and C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic groups may have at most 5 substituents selected from the 5 group consisting of a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a halogen 10 atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a 15 benzyl group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the 20 group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group 25

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and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

5 V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group),

W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups, and

10 each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above),

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different), or

15 R<sup>1</sup> may be a hydrogen atom when Y is bonded at the 4-, 5-, 6- or 7-position of an indole ring,

each of R<sup>2</sup> and R<sup>3</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group (said C<sub>1</sub>-C<sub>7</sub> alkyl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl groups may be substituted with a hydroxyl group), a C<sub>1</sub>-C<sub>7</sub> alkyloxy group, a benzyloxy group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a furanyl group, a thienyl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, a pyranyl group, a quinolyl group, a benzoxazolyl group, a 25 benzothiazolyl group or a benzimidazolyl group (each of said phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

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imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl and benzimidazolyl groups may be substituted with at most 5 substituents selected from the group consisting of a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group and a halogen atom), a hydroxyl group or halogen atom;

5 R<sup>4</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>7</sub> alkyl group, or forms a bond together with R<sup>7</sup>;

R<sup>5</sup> is a hydrogen atom or a carboxymethyl group; and

10 R<sup>n</sup> is a substituent at the 1-positon of an indole ring, examples of which include a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>4</sub> alkoxyethyl group, an aryloxymethyl group, a C<sub>1</sub>-C<sub>4</sub> alkylaminomethyl group, a substituted acetamidemethyl group, a substituted thiomethyl group, a carboxyl group, a C<sub>1</sub>-C<sub>7</sub> acyl group, an arylcarbonyl group, a C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl group, an aryloxycarbonyl group, a C<sub>1</sub>-C<sub>4</sub> alkylaminocarbonyl group, an arylaminocarbonyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkoxyalkyloxy group, a 15 trialkylsilyl group, a trialkylarylsilyl group, an alkylsulfonyl group or an arylsulfonyl group.

20 The substituents of the compound of the formula (I) of the present invention will be explained with reference to typical examples, but it should be understood that the scope of the present invention is by no means limited by these examples.

25 Each substituent in the formula (I) will be

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specifically described hereinafter.

In the definition of R<sup>1</sup>:

R<sup>1</sup> is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position, preferably at the 2- or 5-position of an indole ring.

The C<sub>1</sub>-C<sub>10</sub> alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neo-pentyl, t-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-1-ethyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, 1-heptyl, 2-heptyl, 1-ethyl-1,2-dimethyl-n-propyl, 1-ethyl-2,2-dimethyl-n-propyl, 1-octyl, 3-octyl, 4-methyl-3-n-heptyl, 6-methyl-2-n-heptyl, 2-propyl-1-n-heptyl, 2,4,4-trimethyl-1-n-pentyl, 1-nonyl, 2-nonyl, 2,6-dimethyl-4-n-heptyl, 3-ethyl-2,2-dimethyl-3-n-pentyl, 3,5,5-trimethyl-1-n-hexyl, 1-decyl, 2-decyl, 4-decyl, 3,7-dimethyl-1-n-octyl, and 3,7-dimethyl-3-n-octyl. Preferred is a C<sub>4</sub>-C<sub>10</sub> alkyl group which includes, for example, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neo-pentyl, t-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-1-ethyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, 1-heptyl, 2-heptyl, 1-ethyl-1,2-dimethyl-n-propyl, 1-ethyl-2,2-dimethyl-n-propyl, 1-octyl, 3-octyl, 4-methyl-3-n-heptyl, 6-methyl-2-n-heptyl, 2-propyl-1-n-heptyl, 2,4,4-trimethyl-1-n-pentyl, 1-nonyl, 2-nonyl, 2,6-dimethyl-4-n-

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heptyl, 3-ethyl-2,2-dimethyl-3-n-pentyl, 3,5,5-trimethyl-1-n-hexyl, 1-decyl, 2-decyl, 4-decyl, 3,7-dimethyl-1-n-octyl and 3,7-dimethyl-3-n-octyl. Each group may be substituted by a hydroxyl group or a C<sub>1</sub>-C<sub>7</sub> alkyl group.

5        The C<sub>2</sub>-C<sub>10</sub> alkenyl group includes, for example, ethenyl, 1-propenyl, 2-propenyl, 1-methylvinyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-ethyl-2-vinyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 2,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl, 1-methyl-1-pentenyl, 1-heptenyl, 1-octenyl, 1-nonenyl and 1-decanyl.

10      Preferred is a C<sub>5</sub>-C<sub>10</sub> alkenyl group which includes, for example, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 2,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl, 1-methyl-1-pentenyl, 1-heptenyl, 1-octenyl, 1-nonenyl and 1-decanyl. Each group may be substituted by a hydroxyl group or a C<sub>1</sub>-C<sub>7</sub> alkyl group.

15      The C<sub>2</sub>-C<sub>10</sub> alkynyl group includes, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-

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butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl, 1-nonyl, and 1-decynyl. Preferred is a C<sub>5</sub>-C<sub>10</sub> alkynyl group which includes, for example, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl, 1-nonyl and 1-decynyl. Each group may be substituted by a hydroxyl group or a C<sub>1</sub>-C<sub>7</sub> alkyl group.

The C<sub>1</sub>-C<sub>10</sub> alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy. Preferred is a C<sub>4</sub>-C<sub>10</sub> alkoxy group which includes, for example, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy. Each group may be substituted by a hydroxyl group or a C<sub>1</sub>-C<sub>7</sub> alkyl group.

The C<sub>2</sub>-C<sub>10</sub> alkenyloxy group includes, for example, ethenyloxy, 1-propenyloxy, 2-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 2,4-pentadienyloxy, 1-hexenyloxy, 2-hexenyloxy, 3-hexenyloxy, 4-hexenyloxy, 5-hexenyloxy, 2,4-hexadienyloxy, 1-heptenyloxy, 1-octenyloxy, 1-nonenyloxy and 1-decenyloxy. Preferred is a C<sub>5</sub>-C<sub>10</sub> alkenyloxy which includes, for example, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 2,4-pentadienyloxy, 1-hexenyloxy, 2-hexenyloxy, 3-

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hexenyloxy, 4-hexenyloxy, 5-hexenyloxy, 2,4-hexadienyloxy, 1-heptenyloxy, 1-octenyloxy, 1-nonenyloxy and 1-decenyloxy. Each group may be substituted by a hydroxyl group or a C<sub>1</sub>-C<sub>7</sub> alkyl group.

5 The C<sub>1</sub>-C<sub>10</sub> alkylthio group includes, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-butylthio, t-butylthio, pentylthio, hexylthio, heptylthio, octylthio, nonylthio and decylthio. Preferred is a C<sub>5</sub>-C<sub>10</sub> alkylthio which 10 includes, for example, pentylthio, hexylthio, heptylthio, octylthio, nonylthio and decylthio. Each group may be substituted by a hydroxyl group or a C<sub>1</sub>-C<sub>7</sub> alkyl group.

15 The C<sub>1</sub>-C<sub>10</sub> monoalkylamino group includes, for example, methylamino, ethylamino, n-propylamino, i-propylamino, n-butylamino, i-butylamino, s-butylamino, t-butylamino, pentylamino, hexylamino, heptylaminio, octylamino, nonylamino and decylamino. Preferred is a C<sub>5</sub>-C<sub>10</sub> monoalkylamino group which includes, for example, pentylamino, hexylamino, heptylaminio, octylamino, 20 nonylamino and decylamino. Each group may be substituted by a hydroxyl group or a C<sub>1</sub>-C<sub>7</sub> alkyl group.

25 The di-C<sub>1</sub>-C<sub>10</sub> alkylamino group includes, for example, dimethylamino, diethylamino, di-n-propylamino, di-i-propylamino, di-n-hexylamino, N-methyl-N-n-pentylamino, N-methyl-N-n-hexylamino, N-methyl-N-n-heptylaminio, N-methyl-N-n-octylamino, N-methyl-N-n-nonylaminio, and N-methyl-N-n-decylamino. Preferred are, for example, N-

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methyl-N-n-pentylamino, N-methyl-N-n-hexylamino, N-methyl-N-n-heptylamino, N-methyl-N-n-octylamino, N-methyl-N-n-nonylamino, and N-methyl-N-n-decylamino. Each group may be substituted by a hydroxyl group or a C<sub>1</sub>-C<sub>7</sub> alkyl group.

In the definition of Z:

The C<sub>3</sub>-C<sub>10</sub> cycloalkyl group includes, for example, cyclopropyl, 1-methyl-cyclopropyl, 2-methyl-cyclopropyl, 4-methyl-cyclohexyl, cyclobutyl, cyclopentyl, cyclohexyl, 10 cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 1-adamantyl, and 2-adamantyl. Preferred is a C<sub>6</sub>-C<sub>10</sub> cycloalkyl group which includes, for example, cyclohexyl, bicyclo[2.2.1]heptyl, 15 bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 1-adamantyl and 2-adamantyl. Each group may have at most 5 substituents (the substituents may, for example, be a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a 20 hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide 25 group, a methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy

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group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted 5 with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-10 tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The  $C_3$ - $C_7$  cycloalkenyl group includes, for example, cyclohexenyl (said cyclohexenyl includes 1-cyclohexenyl, 2-cyclohexenyl, and 3-cyclohexenyl), cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl, and 2,5-bicyclo[2.2.1]heptadienyl. Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a  $C_1$ - $C_7$  alkyl group, a  $C_3$ - $C_7$  cycloalkyl group, a  $C_3$ - $C_7$  cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a  $C_1$ - $C_7$  alkoxy group, a  $C_1$ - $C_7$  alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a  $C_1$ - $C_3$  alkoxycarbonyl group, a nitrile group, a carbamoyl

group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, 5 imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a 10 dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C<sub>6</sub>-C<sub>14</sub> aromatic group includes, for example, 15 phenyl, naphthyl (said naphthyl includes  $\alpha$ -naphthyl, and  $\beta$ -naphthyl), indenyl (said indenyl includes 1-indenyl, 2-indenyl, 3-indenyl, 4-indenyl, 5-indenyl, 6-indenyl, and 7-indenyl), indanyl (said indanyl includes 1-indanyl, 2-indanyl, 4-indanyl, and 5-indanyl), and fluorenyl (said 20 fluorenyl includes 1-fluorenyl, 2-fluorenyl, 3-fluorenyl, 4-fluorenyl, and 9-fluorenyl). Preferred is a C<sub>6</sub>-C<sub>14</sub> aromatic group which includes, for example, phenyl, naphthyl (said naphthyl includes  $\alpha$ -naphthyl, and  $\beta$ -naphthyl), and fluorenyl (said fluorenyl includes 1- 25 fluorenyl, 2-fluorenyl, 3-fluorenyl, 4-fluorenyl, and 9-fluorenyl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom,

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a  $C_1$ - $C_7$  alkyl group, a  $C_3$ - $C_7$  cycloalkyl group, a  $C_3$ - $C_7$  cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a  $C_1$ - $C_7$  alkoxy group, a  $C_1$ - $C_7$  alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a  $C_1$ - $C_3$  alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri- $C_1$ - $C_7$ -alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a  $C_1$ - $C_7$  alkyl group, a  $C_3$ - $C_7$  cycloalkyl group, a  $C_1$ - $C_3$  alkoxy group, a  $C_1$ - $C_3$  alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The  $C_1$ - $C_{12}$  heterocyclic aromatic group is a heterocyclic group having a 5-15 membered monocyclic or 25 condensed ring containing at most 5 hetero-atoms in the ring, selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom. Examples of the

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heterocyclic aromatic group include furyl (said furyl includes 2-furyl, and 3-furyl), thienyl (said thienyl includes 2-thienyl, and 3-thienyl), pyrrolyl (said pyrrolyl includes 1-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl), oxazolyl (said oxazolyl includes 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl), thiazolyl (said thiazolyl includes 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl), isoxazolyl (said isoxazolyl includes 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl), isothiazolyl (said isothiazolyl includes 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl), furazanyl (said furazanyl includes 3-furazanyl), pyrazolyl (said pyrazolyl includes 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl), oxopyrazolyl (said oxopyrazolyl includes 3-oxopyrazol-1-yl, 3-oxopyrazol-2-yl, 3-oxopyrazol-3-yl, 3-oxopyrazol-4-yl, and 4-oxopyrazol-3-yl), imidazolyl (said imidazolyl includes 1-imidazolyl, 2-imidazolyl, and 4-imidazolyl), oxoimidazolyl (said oxoimidazolyl includes 2-oxoimidazol-1-yl, and 2-oxoimidazol-4-yl), triazolyl (said triazolyl includes 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, and 1,2,4-triazol-4-yl), triazolonyl (said triazolonyl includes 1,2,4(2H,4H)-triazol-3-on-2-yl, 1,2,4-(2H,4H)-triazol-3-on-4-yl, 1,2,4(2H,4H)-triazol-3-on-5-yl, 1,2,4(1H,2H)-triazol-3-on-1-yl, 1,2,4(1H,2H)-triazol-3-on-2-yl, and 1,2,4(1H,2H)-triazol-3-on-5-yl), tetrazolyl (said tetrazolyl includes 1-tetrazolyl, 2-tetrazolyl, and

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5-tetrazolyl), pyranyl (said pyranyl includes 2-pyranyl, 3-pyranyl, and 4-pyranyl), pyridyl (said pyridyl includes 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyridonyl (said pyridonyl includes 2-pyridon-1-yl, 2-pyridon-3-yl, 2-pyridon-4-yl, 2-pyridon-5-yl, 2-pyridon-6-yl, 4-pyridon-1-yl, 4-pyridon-2-yl, and 4-pyridon-3-yl), pyridazinyl (said pyridazinyl includes 3-pyridazinyl, and 4-pyridazinyl), pyridazinonyl (said pyridazinonyl includes 3(2H)-pyridazinon-2-yl, 3(2H)-pyridazinon-4-yl, 3(2H)-pyridazinon-5-yl, 3(2H)-pyridazinon-6-yl, 4(1H)-pyridazinon-1-yl, 4(1H)-pyridazinon-3-yl, 4(1H)-pyridazinon-5-yl, and 4(1H)-pyridazinon-6-yl), pyrimidinyl (said pyrimidinyl includes 2-pyrimidinyl, 4-pyrimidinyl, and 5-pyrimidinyl), pyrimidinonyl (said pyrimidinonyl includes (2(1H)-pyrimidinon-1-yl, 2(1H)-pyrimidinon-4-yl, 2(1H)-pyrimidinon-5-yl, 2(1H)-pyrimidinon-6-yl, 4(3H)-pyrimidinon-2-yl, 4(3H)-pyrimidinon-3-yl, 4(3H)-pyrimidinon-5-yl, 4(3H)-pyrimidinon-6-yl, 4(1H)-pyrimidinon-1-yl, 4(1H)-pyrimidinon-2-yl, 4(1H)-pyrimidinon-5-yl, and 4(1H)-pyrimidinon-6-yl), pyrazinyl (said pyrazinyl includes 2-pyrazinyl, 2(1H)-pyrazin-1-yl, 2(1H)-pyrazin-3-yl, 2(1H)-pyrazin-5-yl, and 2(1H)-pyrazin-6-yl), triazinyl (said triazinyl includes 1,2,3-triazin-4-yl, 1,2,3-triazin-5-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, and 1,2,4-triazin-6-yl), tetrazinyl (said tetrazinyl includes 1,2,3,4-tetrazin-5-yl, and 1,2,4,5-tetrazin-3-yl),

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indolyl (said indolyl includes 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, and 7-indolyl), quinolyl (said quinolyl includes 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-quinolyl), quinolonyl (said quinolonyl includes 2-quinolone-1-yl, 2-quinolone-3-yl, 2-quinolone-4-yl, 2-quinolone-5-yl, 2-quinolone-6-yl, 2-quinolone-7-yl, 2-quinolone-8-yl, 4-quinolone-1-yl, 4-quinolone-2-yl, 4-quinolone-3-yl, 4-quinolone-5-yl, 4-quinolone-6-yl, 4-quinolone-7-yl, and 4-quinolone-8-yl), benzofuranyl (said benzofuranyl includes 2-benzofuranyl, 3-benzofuranyl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, and 7-benzofuranyl), benzothienyl (said benzothienyl includes 2-benzothienyl, 3-benzothienyl, 4-benzothienyl, 5-benzothienyl, 6-benzothienyl, and 7-benzothienyl), isoquinolyl (said isoquinolyl includes 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, and 8-isoquinolyl), isoquinolonyl (said isoquinolonyl includes 1-isoquinolone-2-yl, 1-isoquinolone-3-yl, 1-isoquinolone-4-yl, 1-isoquinolone-5-yl, 1-isoquinolone-6-yl, 1-isoquinolone-7-yl, 1-isoquinolone-8-yl, 3-isoquinolone-2-yl, 3-isoquinolone-4-yl, 3-isoquinolone-5-yl, 3-isoquinolone-6-yl, 3-isoquinolone-7-yl, and 3-isoquinolone-8-yl), benzoxazolyl (said benzoxazolyl includes 2-benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, and 7-benzoxazolyl), benzothiazolyl (said benzothiazolyl includes 2-benzothiazolyl, 4-

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benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, and 7-benzothiazolyl), benzopyrazolyl (said benzopyrazolyl includes 1-benzopyrazolyl, 2-benzopyrazolyl, 3-benzopyrazolyl, 4-benzopyrazolyl, 5-benzopyrazolyl, 6-benzopyrazolyl, and 7-benzopyrazolyl), benzimidazolyl (said benzimidazolyl includes 1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, and 5-benzimidazolyl), benzotriazolyl (said benzotriazolyl includes 1-benzotriazolyl, 4-benzotriazolyl, and 5-benzotriazolyl), 10 benzopyranyl (said benzopyranyl includes 2-benzopyranyl, 3-benzopyranyl, 4-benzopyranyl, 5-benzopyranyl, 6-benzopyranyl, 7-benzopyranyl, and 8-benzopyranyl), indolizinyl (said indolizinyl includes 1-indolizinyl, 2-indolizinyl, 3-indolizinyl, 5-indolizinyl, 6-indolizinyl, 15 7-indolizinyl, and 8-indolizinyl), purinyl (said purinyl includes 2-purinyl, 6-purinyl, 7-purinyl, and 8-purinyl), phthalazinyl (said phthalazinyl includes 1-phthalazinyl, 5-phthalazinyl, and 6-phthalazinyl), oxophthalazinyl (said oxophthalazinyl includes 1-oxophthalazin-2-yl, 1-oxophthalazin-4-yl, 1-oxophthalazin-5-yl, 1-oxophthalazin-6-yl, 1-oxophthalazin-7-yl, and 1-oxophthalazin-8-yl), naphthyridinyl (said naphthyridinyl includes 2-naphthyridinyl, 3-naphthyridinyl, and 4-naphthyridinyl), quinoxalinyl (said quinoxalinyl includes 2-quinoxalinyl, 5-quinoxalinyl, and 6-quinoxalinyl), 25 quinazolinyl (said quinazolinyl includes 2-quinazolinyl, 4-quinazolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-

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quinazolinyl, and 8-quinazolinyl), cinnolinyl (said cinnolinyl includes 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, and 8-cinnolinyl), benzodioxolyl (said benzodioxolyl includes 5 1,3-benzodioxol-4-yl, and 1,3-benzodioxol-5-yl), benzodioxanyl (said benzodioxanyl includes 1,4-benzodioxan-2-yl, 1,4-benzodioxan-5-yl, and 1,4-benzodioxan-6-yl), oxonaphthalenyl (said oxonaphthalenyl includes 1,4-oxonaphthalen-2-yl, 1,4-oxonaphthalen-5-yl, 10 and 1,4-oxonaphthalen-6-yl), 2,3-dihydrobenzofuranyl (said 2,3-dihydrobenzofuranyl includes 2,3-dihydro-4-benzofuranyl, 2,3-dihydro-5-benzofuranyl, 2,3-dihydro-6-benzofuranyl, and 2,3-dihydro-7-benzofuranyl), benzothiazinyl (said benzothiazinyl includes 1,4-benzothiazin-2-yl, 1,4-benzothiazin-3-yl, 1,4-benzothiazin-4-yl, 1,4-benzothiazin-5-yl, 1,4-benzothiazin-6-yl, 1,4-benzothiazin-7-yl, and 1,4-benzothiazin-8-yl), pteridinyl (said pteridinyl includes 15 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, and 7-pteridinyl), pyrazolo[1,5-a]pyrimidinyl (said pyrazolo[1,5-a]pyrimidinyl includes pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-3-yl, pyrazolo[1,5-a]pyrimidin-5-yl, pyrazolo[1,5-a]pyrimidin-6-yl, and pyrazolo[1,5-a]pyrimidin-7-yl), pyrazolo[5,1-c][1,2,4]triazinyl (said pyrazolo[5,1-c][1,2,4]triazinyl includes 20 pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrazolo[5,1-c][1,2,4]triazin-4-yl, pyrazolo[5,1-c][1,2,4]triazin-5-yl, pyrazolo[5,1-c][1,2,4]triazin-6-yl, and pyrazolo[5,1-c][1,2,4]triazin-7-yl), pyrazolo[5,1-c][1,2,4]triazin-8-yl, and pyrazolo[5,1-c][1,2,4]triazin-9-yl), and 25 pyrazolo[5,1-c][1,2,4]triazin-10-yl, pyrazolo[5,1-c][1,2,4]triazin-11-yl, pyrazolo[5,1-c][1,2,4]triazin-12-yl, pyrazolo[5,1-c][1,2,4]triazin-13-yl, pyrazolo[5,1-c][1,2,4]triazin-14-yl, pyrazolo[5,1-c][1,2,4]triazin-15-yl, pyrazolo[5,1-c][1,2,4]triazin-16-yl, and pyrazolo[5,1-c][1,2,4]triazin-17-yl).

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c][1,2,4]triazin-7-yl, and pyrazolo[5,1-c][1,2,4]triazin-8-yl), thiazolo[3,2-b]triazolyl (said thiazolo[3,2-b]triazolyl includes thiazolo[3,2-b]triazol-2-yl, thiazolo[3,2-b]triazol-5-yl, and thiazolo[3,2-b]triazol-6-yl), benzopyrano[2,3-b]pyridyl (said benzopyrano[2,3-b]pyridyl includes benzopyrano[2,3-b]pyridin-2-yl, benzopyrano[2,3-b]pyridin-3-yl, benzopyrano[2,3-b]pyridin-4-yl, benzopyrano[2,3-b]pyridin-5-yl, benzopyrano[2,3-b]pyridin-6-yl, benzopyrano[2,3-b]pyridin-7-yl, benzopyrano[2,3-b]pyridin-8-yl, and benzopyrano[2,3-b]pyridin-9-yl), 5H-benzopyrano[2,3-b]pyridonyl (said 5H-benzopyrano[2,3-b]pyridonyl includes 5H-benzopyrano[2,3-b]pyridin-5-on-2-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-3-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-4-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-6-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-7-yl, and 5H-benzopyrano[2,3-b]pyridin-5-on-8-yl), xanthenyl (said xanthenyl includes 1-xanthenyl, 2-xanthenyl, 3-xanthenyl, 4-xanthenyl, and 9-xanthenyl), phenoxythiinyl (said phenoxythiinyl includes 1-phenoxythiinyl, 2-phenoxythiinyl, 3-phenoxythiinyl, and 4-phenoxythiinyl), carbazolyl (said carbazolyl includes 1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl, and 9-carbazolyl), acridinyl (said acridinyl includes 1-acridinyl, 2-acridinyl, 3-acridinyl, 4-acridinyl, and 9-acridinyl), phenazinyl (said phenazinyl includes 1-phenazinyl, 2-phenazinyl, 3-phenazinyl, and 4-

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phenazinyl), phenothiazinyl (said phenothiazinyl includes 1-phenothiazinyl, 2-phenothiazinyl, 3-phenothiazinyl, 4-phenothiazinyl, and 10-phenothiazinyl), phenoazinyl (said phenoazinyl includes 1-phenoazinyl, 2-phenoazinyl, 3-phenoazinyl, 4-phenoazinyl, and 10-phenoazinyl), and thianthrenyl (said thianthrenyl includes 1-thianthrenyl, 2-thianthrenyl, 3-thianthrenyl, 4-thianthrenyl, 6-thianthrenyl, 7-thianthrenyl, 8-thianthrenyl, and 9-thianthrenyl). Preferred examples of the C<sub>1</sub>-C<sub>12</sub> heterocyclic aromatic group include furyl (said furyl includes 2-furyl, and 3-furyl), thienyl (said thienyl includes 2-thienyl, and 3-thienyl), pyrrolyl (said pyrrolyl includes 1-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl), oxazolyl (said oxazolyl includes 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl), thiazolyl (said thiazolyl includes 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl), isoxazolyl (said isoxazolyl includes 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl), isothiazolyl (said isothiazolyl includes 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl), imidazolyl (said imidazolyl includes 1-imidazolyl, 2-imidazolyl, and 4-imidazolyl), pyridyl (said pyridyl includes 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyridazinyl (said pyridazinyl includes 3-pyridazinyl, and 4-pyridazinyl), pyridazinonyl (said pyridazinonyl includes 3(2H)-pyridazinon-2-yl, 3(2H)-pyridazinon-4-yl, 3(2H)-pyridazinon-5-yl, and 3(2H)-pyridazinon-6-yl), pyrimidinyl (said pyrimidinyl includes

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2-pyrimidinyl, 4-pyrimidinyl, and 5-pyrimidinyl),  
pyrazinyl (said pyrazinyl includes 2-pyrazinyl), indolyl  
(said indolyl includes 1-indolyl, 2-indolyl, 3-indolyl,  
4-indolyl, 5-indolyl, 6-indolyl, and 7-indolyl), quinolyl  
5 (said quinolyl includes 2-quinolyl, 3-quinolyl, 4-  
quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-  
quinolyl), benzoxazolyl (said benzoxazolyl includes 2-  
benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-  
benzoxazolyl, and 7-benzoxazolyl), benzothiazolyl (said  
10 benzothiazolyl includes 2-benzothiazolyl, 4-  
benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, and  
7-benzothiazolyl), benzimidazolyl (said benzimidazolyl  
includes 1-benzimidazolyl, 2-benzimidazolyl, 4-  
benzimidazolyl, and 5-benzimidazolyl), phthalazinyl (said  
15 phthalazinyl includes 1-phthalazinyl, 5-phthalazinyl, and  
6-phthalazinyl), quinoxalinyl (said quinoxalinyl includes  
2-quinoxalinyl, 5-quinoxalinyl, and 6-quinoxalinyl),  
benzodioxolyl (said benzodioxolyl includes 1,3-  
benzodioxol-4-yl, and 1,3-benzodioxol-5-yl),  
20 benzothiazinyl (said benzothiazinyl includes 1,4-  
benzothiazin-2-yl, 1,4-benzothiazin-3-yl, 1,4-  
benzothiazin-4-yl, 1,4-benzothiazin-5-yl, 1,4-  
benzothiazin-6-yl, 1,4-benzothiazin-7-yl, and 1,4-  
benzothiazin-8-yl), pyrazolo[1,5-a]pyrimidinyl (said  
25 pyrazolo[1,5-a]pyrimidinyl includes pyrazolo[1,5-  
a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-3-yl,  
pyrazolo[1,5-a]pyrimidin-5-yl, pyrazolo[1,5-a]pyrimidin-

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6-yl, and pyrazolo[1,5-a]pyrimidin-7-yl), pyrazolo[5,1-c][1,2,4]triazinyl (said pyrazolo[5,1-c][1,2,4]triazinyl includes pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrazolo[5,1-c][1,2,4]triazin-4-yl, pyrazolo[5,1-c][1,2,4]triazin-7-yl, and pyrazolo[5,1-c][1,2,4]triazin-8-yl), thiazolo[3,2-b]triazolyl (said thiazolo[3,2-b]triazolyl includes thiazolo[3,2-b]triazol-2-yl, thiazolo[3,2-b]triazol-5-yl, and thiazolo[3,2-b]triazol-6-yl), and benzopyrano[2,3-b]pyridyl (said 10 benzopyrano[2,3-b]pyridyl includes benzopyrano[2,3-b]pyridin-2-yl, benzopyrano[2,3-b]pyridin-3-yl, benzopyrano[2,3-b]pyridin-4-yl, benzopyrano[2,3-b]pyridin-5-yl, benzopyrano[2,3-b]pyridin-6-yl, benzopyrano[2,3-b]pyridin-7-yl, benzopyrano[2,3-b]pyridin-8-yl, and benzopyrano[2,3-b]pyridin-9-yl).

Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and 20 cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a 25 methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a

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tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted 5 with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3- 10 tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic group is a heterocyclic group having a 3-8 membered monocyclic or 15 condensed dicyclic ring containing at most 3 hetero-atoms in the ring, selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom. Examples of the heterocycloaliphatic group include piperidyl (said piperidyl includes 1-piperidyl, 2-piperidyl, 3-piperidyl, 20 and 4-piperidyl), pyrrolidinyl (said pyrrolidinyl includes 1-pyrrolidinyl, 2-pyrrolidinyl, and 3-pyrrolidinyl), imidazolidinyl (said imidazolidinyl includes 1-imidazolidinyl, 2-imidazolidinyl, and 4-imidazolidinyl), pyrazolidinyl (said pyrazolidinyl 25 includes 1-pyrazolidinyl, 3-pyrazolidinyl, and 4-pyrazolidinyl), morpholinyl (said morpholinyl includes 2-morpholinyl, 3-morpholinyl, and 4-morpholinyl), and

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tetrahydrofuryl (said tetrahydrofuryl includes 2-tetrahydrofuryl, and 3-tetrahydrofuryl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a 5 C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino 10 group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a 15 phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub>, 20 cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a 25 thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

In the definitions of R<sup>a</sup>, R<sup>b</sup> and R<sup>c</sup>:

The C<sub>1</sub>-C<sub>7</sub> alkyl group includes, for example, methyl,

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ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, and n-heptyl. Preferred are methyl, ethyl and n-propyl. Each group may be substituted with a hydroxyl group.

5 The  $C_3$ - $C_7$  cycloalkyl group includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, and bicyclo[3.1.1]heptyl. Preferred are cyclopropyl and cyclohexyl. Each group may be substituted by a hydroxyl  
10 group.

The  $C_3$ - $C_7$  cycloalkenyl group includes, for example, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl and 2,5-bicyclo[2.2.1]heptadienyl. Each group may be substituted  
15 by a hydroxyl group.

The  $C_1$ - $C_7$  alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy and heptyloxy.

20 The  $C_1$ - $C_7$  alkylthio group includes, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-buthylthio, t-butylthio, pentylthio, hexylthio and heptylthio.

The tri- $C_1$ - $C_7$ -alkylsilyloxy group includes, for  
25 example, trimethylsilyloxy, triethylsilyloxy, triisopropylsilyloxy, diethylisopropylsilyloxy, dimethylisopropylsilyloxy, di-t-butylmethysilyloxy,

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isopropyldimethylsilyloxy, t-butyldimethylsilyloxy, thexyldimethylsilyloxy or the like, preferably t-butyldimethylsilyloxy or the like.

The naphthyl group includes an  $\alpha$ -naphthyl group, a  $\beta$ -naphthyl group. The furanyl group includes a 2-furanyl group and a 3-furanyl group. The thiienyl group includes a 2-thienyl group and a 3-thienyl group. The imidazolyl group includes a 1-imidazolyl group, a 2-imidazolyl group and a 4-imidazolyl group. The pyridyl group includes a 2-pyridyl group and a 3-pyridyl group and a 4-pyridyl group. Each groups may be substituted with at most 5 substituents selected from the group consisting of a  $C_1-C_7$  alkyl group, a  $C_3-C_7$  cycloalkyl group, a  $C_1-C_3$  alkoxy group, a  $C_1-C_3$  alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group.

The phenyl and the benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a  $C_1-C_7$  alkyl group, a  $C_3-C_7$  cycloalkyl group, a  $C_1-C_3$  alkoxy group, a  $C_1-C_3$  alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group.

The  $C_1-C_3$  alkoxy carbonyl group includes, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl and i-propoxycarbonyl.

The halogen atom includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. Preferred are a

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fluorine atom, a chlorine atom and a bromine atom.

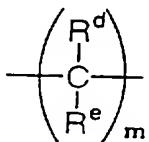
V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or C<sub>1</sub>-C<sub>3</sub> alkyl (which may, for example, be methyl, ethyl, n-propyl or i-propyl, preferably methyl)). It is 5 preferably S, SO, SO<sub>2</sub> or NR<sup>8</sup>.

W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be substituted with at most 3, preferably at most 2, of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups.

10 The C<sub>1</sub>-C<sub>7</sub> alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl. Preferred may, for example, be methyl.

W is preferably

15



wherein m is from 1 to 5, and each of R<sup>d</sup> and R<sup>e</sup> is a 20 hydrogen atom, a methyl group or a hydroxyl group, or R<sup>d</sup> and R<sup>e</sup> together form an oxo group, or adjacent R<sup>d</sup>'s together form a double bond, or adjacent R<sup>d</sup>'s and R<sup>e</sup>'s together form a triple bond (provided that R<sup>d</sup> and R<sup>e</sup> on the first carbon atom adjacent to N are not hydroxyl groups and provided that R<sup>d</sup> and R<sup>e</sup> on the first carbon 25 atom adjacent to O are not hydroxyl groups or do not together form an oxo group).

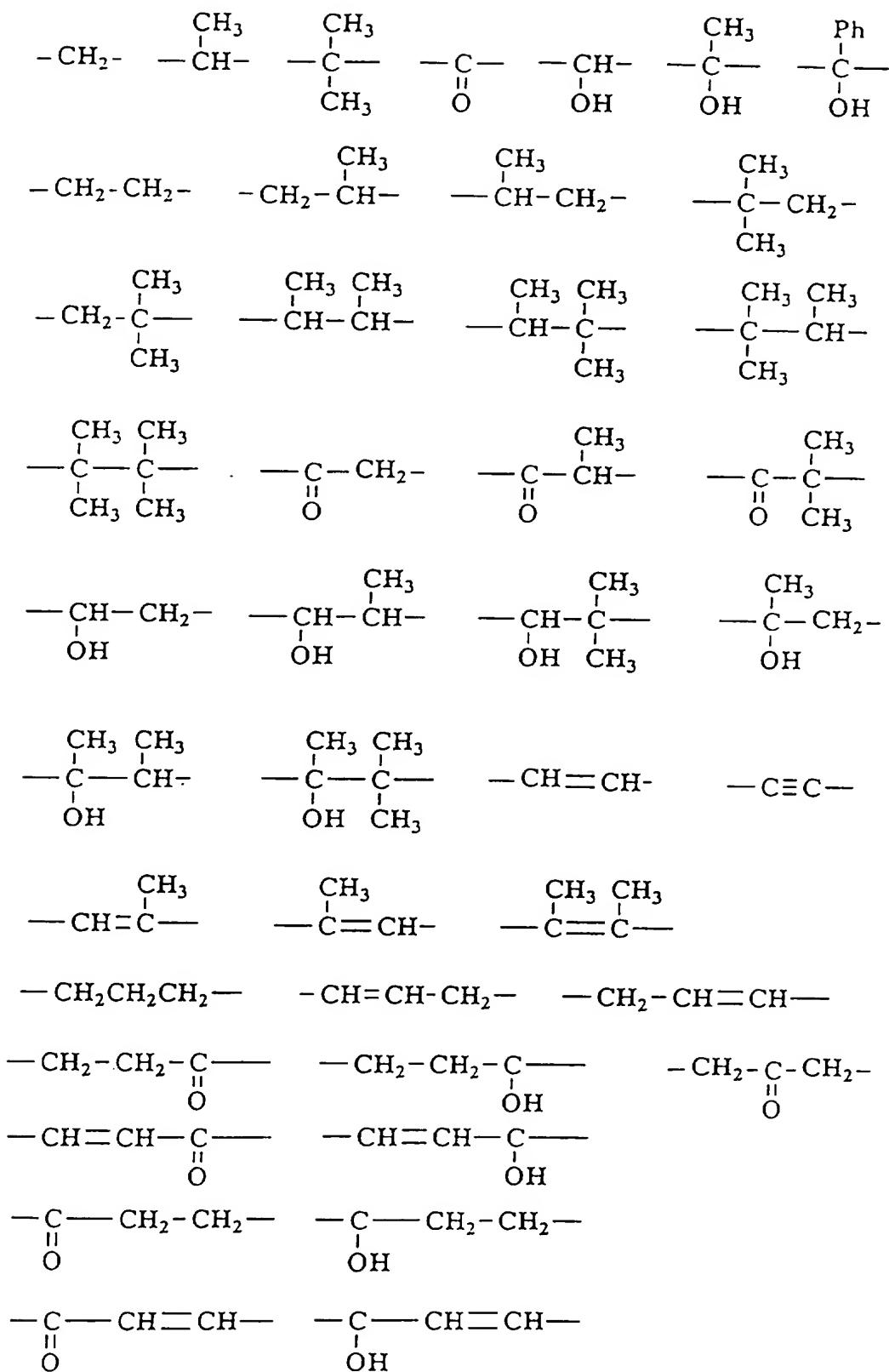
R<sup>1</sup> may be -W<sub>k</sub>-V<sub>l</sub>-Z, -V-W-Z or -W-V-W-Z in addition to

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the one mentioned above.

$-W_k - V_\ell - Z$  may, for example, be  $-W - Z$ ,  $-V - Z$  or  $-W - V - Z$ .

Preferable examples of  $-W-$  in the above  $-W - Z$  are illustrated below.



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Also, preferable examples of -V- in the above -V-Z include S, SO and SO<sub>2</sub>.

Also, preferable examples of -W-V- in the above -W-V-Z include -CO-NR<sup>8</sup>- (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group (e.g. methyl, ethyl, n-propyl or i-propyl, preferably methyl)).

Also, preferable examples of -V-W- in the above -V-W-Z include -O-(CH<sub>2</sub>)<sub>n</sub>- (n is from 1 to 5).

Also, preferable examples of -W-V-W- in the above -W-V-W-Z include -(CH<sub>2</sub>)<sub>n</sub>-NR<sup>8</sup>-CO- (n is from 1 to 5, R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group (e.g. methyl, ethyl, n-propyl or i-propyl, preferably methyl)).

Each of R<sup>2</sup> and R<sup>3</sup> independently is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl, and said C<sub>1</sub>-C<sub>7</sub> alkyl group may be substituted with at most two hydroxyl groups, preferably one hydroxyl group), a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl or bicyclo[3.1.1]heptyl, preferably cyclopropyl or cyclohexyl, and said C<sub>3</sub>-C<sub>7</sub> cycloalkyl group may be substituted with at most 2 hydroxyl group, preferably one hydroxyl group), a C<sub>1</sub>-C<sub>7</sub> alkoxy group (which may, for example, be methoxy, ethoxy n-propoxy, i-propoxy, n-

butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy or heptyloxy, preferably methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy or t-butoxy), a 5  
benzyloxy group, a phenyl group, a naphthyl group (which  
may be an  $\alpha$ -naphthyl group, or a  $\beta$ -naphthyl group), a  
benzyl group, a pyridyl group (which may, for example, be  
a 2-pyridyl group, a 3-pyridyl group or a 4-pyridyl  
group, preferably a 2-pyridyl group), a pyrimidinyl group  
(which may, for example, be a 2-pyrimidinyl group, a 4-  
10 pyrimidinyl group or a 5-pyrimidinyl group), a  
pyridazinyl group (which may, for example, be a 3-  
pyridazinyl group or a 4-pyridazinyl group), a furanyl  
group (which may, for example, be a 2-furanyl group or a  
3-furanyl group), a thienyl group (which may, for  
15 example, be a 2-thienyl group or a 3-thienyl group), a  
pyrrolyl group (which may, for example, be a 1-pyrrolyl  
group, a 2-pyrrolyl group or a 3-pyrrolyl group), a  
pyrazolyl group (which may, for example, be a 1-pyrazolyl  
group, a 3-pyrazolyl group or a 4-pyrazolyl group), an  
20 imidazolyl group (which may, for example, be a 1-  
imidazolyl group, a 2-imidazolyl group or a 4-imidazolyl  
group), a pyranyl group (which may, for example, be 2-  
pyranyl, 3-pyranyl or 4-pyranyl, preferably 2-pyranyl), a  
quinolyl group (which may, for example, be 2-quinolyl, 3-  
25 quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl  
or 8-quinolyl, preferably 2-quinolyl), a benzoxazolyl  
group (which may, for example, be a 2-benzoxazolyl group, a

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4-benzoxazolyl group, a 5-benzoxazolyl group, a 6-benzoxazolyl group or a 7-benzoxazolyl group, preferably a 2-benzoxazolyl group), a benzothiazolyl group (which may, for example, be a 2-benzothiazolyl group, a 4-5 benzothiazolyl group, a 5-benzothiazolyl group, a 6-benzothiazolyl group or a 7-benzothiazolyl group, preferably a 2-benzothiazolyl group), or a benzimidazolyl group (which may, for example, be a 1-benzimidazolyl group, a 2-benzimidazolyl group, a 4-benzimidazolyl group 10 or a 5-benzimidazolyl group, preferably a 2-benzimidazolyl group).

When R<sup>2</sup> or R<sup>3</sup> is a phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, 15 benzothiazolyl, or benzimidazolyl group, the substituents for such a phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl group may be as follows.

20 The C<sub>1</sub>-C<sub>7</sub> alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl. Preferred may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl.

25 The C<sub>1</sub>-C<sub>7</sub> alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy and

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heptyloxy. Preferred may, for example, be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy or t-butoxy.

The halogen atom may, for example, be a fluorine 5 atom, a chlorine atom, a bromine atom or an iodine atom, preferably, a fluorine atom, a chlorine atom or a bromine atom.

R<sup>4</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>7</sub> alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, 10 n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl), or forms a bond together with R<sup>7</sup>. It is preferably a hydrogen atom or a methyl group, or forms a bond together with R<sup>7</sup>. More preferably, it is a hydrogen atom, or forms a bond 15 together with R<sup>7</sup>.

R<sup>5</sup> is a hydrogen atom or a carboxymethyl group, preferably a hydrogen atom.

R<sup>n</sup> is a substituent at the 1-position of an indole ring, and is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group (such 20 as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl, preferably a C<sub>1</sub>-C<sub>3</sub> alkyl group), a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group (such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, preferably cyclopropyl), a C<sub>1</sub>-C<sub>4</sub> alkoxyethyl group (such as MOM: methoxymethyl, MEM: 2-methoxyethoxymethyl, ethoxymethyl, n-propoxymethyl, i-propoxymethyl, n-butoxymethyl, iBM: isobutyloxymethyl,

BUM: *t*-butoxymethyl, POM: pivaloyloxymethyl and SEM:  
trimethylsilylethoxymethyl, preferably a C<sub>1</sub>-C<sub>2</sub> alkoxy  
methyl group), an aryloxymethyl group (such as BOM:  
benzyloxymethyl, PMBM: *p*-methoxybenzyloxymethyl and *p*-  
5 AOM: *p*-anisyloxymethyl, preferably a benzyloxymethyl  
group), a C<sub>1</sub>-C<sub>4</sub> alkylaminomethyl group (such as  
dimethylaminomethyl), a substituted acetamidemethyl group  
(such as Acm: acetamidemethyl and Tacm:  
trimethylacetamidemethyl), a substituted thiomethyl group  
10 (such as MTM: methylthiomethyl, PTM: phenylthiomethyl and  
Btm: benzylthiomethyl), a carboxyl group, a C<sub>1</sub>-C<sub>7</sub> acyl  
group (such as formyl, acetyl, fluoroacetyl,  
difluoroacetyl, trifluoroacetyl, chloroacetyl,  
dichloroacetyl, trichloroacetyl, propionyl, Pv: pivaloyl  
15 and tigloyl), an arylcarbonyl group (such as benzoyl,  
benzoylformyl, benzoylpropionyl and phenylpropionyl), a  
C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl group (such as methoxycarbonyl,  
ethoxycarbonyl, *n*-propoxycarbonyl, *i*-propoxycarbonyl, *n*-  
butoxycarbonyl, *i*-butoxycarbonyl, BOC: *t*-butoxycarbonyl,  
20 AOC: *t*-amyloxycarbonyl, VOC: vinyloxycarbonyl, AOC:  
allyloxycarbonyl, Teoc: 2-(trimethylsilyl)ethoxycarbonyl,  
and Troc: 2,2,2-trichloroethoxycarbonyl, preferably  
methoxycarbonyl), an aryloxycarbonyl group (such as Z:  
benzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl and MOZ: *p*-  
25 methoxybenzyloxycarbonyl), a C<sub>1</sub>-C<sub>4</sub> alkylaminocarbonyl  
group (such as methylcarbamoyl, Ec: ethylcarbamoyl and *n*-  
propylcarbamoyl), an arylaminocarbonyl group (such as

phenylcarbamoyl), a C<sub>1</sub>-C<sub>7</sub> alkoxy group (such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentoxy, n-hexyloxy and n-heptyloxy, preferably a C<sub>1</sub>-C<sub>3</sub> alkoxy group), a C<sub>1</sub>-C<sub>7</sub> alkoxyalkyloxy group (such as MOMO: methoxymethyloxy, MEMO: methoxyethyloxymethyloxy and BOMO: benzyloxymethyloxy), a trialkylsilyl group (such as TMS: trimethylsilyl, TES: triethylsilyl, TIPS: triisopropylsilyl, DEIPS: diethylisopropylsilyl, DMIPS: dimethylisopropylsilyl, 10 DTBMS: di-t-butyldimethylsilyl, IPDMS: isopropyldimethylsilyl, TBDMS: t-butyldimethylsilyl and TDS: thexyldimethylsilyl, preferably t-butyldimethylsilyl), a trialkylarylsilyl group (such as DPMS: diphenylmethyldimethylsilyl, TBDPS: t-butyldiphenylsilyl, 15 TBMPS: t-butyldimethoxyphenylsilyl and TPS: triphenylsilyl), an alkylsulfonyl group (such as Ms: methane sulfonyl and ethane sulfonyl), and an aryl sulfonyl group (such as benzene sulfonyl, Ts: p-toluene sulfonyl, p-chlorobenzene sulfonyl, MBS: p-methoxybenzene sulfonyl, m-nitrobenzene sulfonyl, iMds: 2,6-dimethoxy-4-methylbenzene sulfonyl, Mds: 2,6-dimethyl-4-methoxybenzene sulfonyl, Mt<sub>b</sub>: 2,4,6-trimethoxybenzene sulfonyl, Mte: 2,3,5,6-tetramethyl-4-methoxybenzene sulfonyl, Mtr: 2,3,6-trimethyl-4-methoxybenzene sulfonyl, 20 Mts: 2,4,6-trimethylbenzene sulfonyl and Pme: pentamethylbenzene sulfonyl), preferably a hydrogen atom, methyl, ethyl, n-propyl, i-propyl, cyclopropyl, methoxy, 25

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ethoxy, n-propoxy, i-propoxy, methoxymethyl, ethoxymethyl, carboxyl and methoxycarbonyl, preferably a hydrogen atom, methyl, methoxymethyl, carboxyl and methoxycarbonyl.

5 Y is bonded on the carbon atom at the 2-, 3-, 4-, 5-, 6- or 7-position of the indole ring, more preferably on the carbon atom at the 2- or 5-position.

In the definition of Y:

10 R<sup>6</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl) or a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably 15 cyclopropyl). It is preferably a hydrogen atom or methyl, more preferably a hydrogen atom.

20 R<sup>7</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl) or a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl), or forms a bond together with R<sup>4</sup>. It is 25 preferably a hydrogen atom, or forms a bond together with R<sup>4</sup>.

X<sup>1</sup> is S or O, preferably S.

X<sup>2</sup> is S, O or NH, preferably O or S, more preferably

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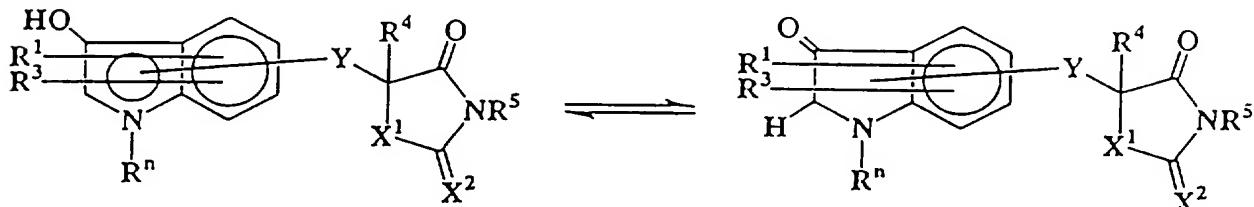
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In the present specification, "n" means normal, "i" means iso, "s" means secondary, "t" means tertiary, "c" means cyclo, "Me" means methyl, "Et" means ethyl, "Pr" 5 means propyl, "Bu" means butyl, "Pen" means pentyl, "Hex" means hexyl, "Ph" means phenyl, and "Hal" means halogen.

Among these compounds, there is a compound having an asymmetric carbon atom at the 5-position of thiazolidine ring. The compound having the above formula (I) includes 10 all of these optical isomers and their mixtures.

When  $R^2$  is a substituent at the 3-position of an indole ring and is a hydroxyl group, the following tautomer may form between the 2-position and the 3-position of an indole ring. The present invention 15 includes all of these tautomers.

Indole type thiazolidines of the following formula and their salts.



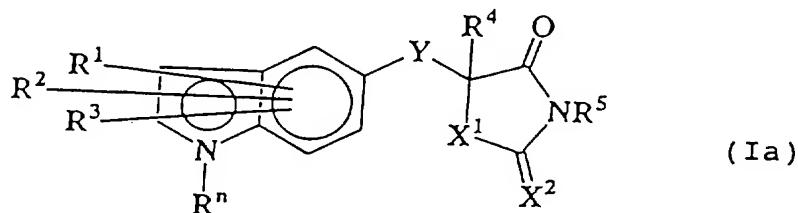
(wherein  $X^1$ ,  $X^2$ ,  $Y$ ,  $R^4$ ,  $R^5$  and  $R^n$  are substituents as defined in the formula (I);  $R^1$  is a substituent at the 2-, 4-, 5-, 6- or 7-position of an indole ring and is a substituent as defined in the formula (I);  $R^2$  is a hydroxyl group at the 3-position of an indole ring; and 25

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$R^3$  is a substituent at the 2-, 4-, 5-, 6- or 7-position of an indole ring and is a substituent as defined in the formula (I)).

The following compounds (1) to (24) may be mentioned 5 as preferred examples of the compound of the formula (I) of the present invention.

(1) The indole type thiazolidine compound and its salt of the present invention, wherein the compound of the formula (I) is represented by the following formula 10 (Ia) :



15 wherein  $R^1$  is a substituent at the 2-, 3-, 4-, 6- or 7-position of an indole ring, and is a hydrogen atom, a  $C_1-C_{10}$  alkyl group, a  $C_2-C_{10}$  alkenyl group, a  $C_2-C_{10}$  alkynyl group, a  $C_1-C_{10}$  alkoxy group, a  $C_2-C_{10}$  alkenyloxy group, a  $C_1-C_{10}$  alkylthio group, a  $C_1-C_{10}$  monoalkylamino group or a 20 di- $C_1-C_{10}$  alkylamino group (each of said  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{10}$  alkynyl,  $C_1-C_{10}$  alkoxy,  $C_2-C_{10}$  alkenyloxy,  $C_1-C_{10}$  alkylthio,  $C_1-C_{10}$  monoalkylamino and di- $C_1-C_{10}$  alkylamino groups may be substituted with a hydroxyl group or a  $C_1-C_7$  alkyl group), or 25  $-W_k-W_t-Z$  (among groups of  $Z$  as defined for the formula (I), said  $C_3-C_{10}$  cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

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cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl,  
bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl,  
said C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group is cyclohexenyl,  
cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl or 2,5-  
5 bicyclo[2.2.1]heptadienyl, said C<sub>6</sub>-C<sub>14</sub> aromatic group is  
phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C<sub>1</sub>-  
C<sub>12</sub> heterocyclic aromatic group is furyl, thieryl,  
pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl,  
furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl,  
10 oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl,  
pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl,  
pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl,  
tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl,  
benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl,  
15 benzothiazolyl, benzopyrazolyl, benzimidazolyl,  
benzotriazolyl, benzopyranyl, indolizinyl, purinyl,  
phthalazinyl, oxophthalazinyl, naphthyridinyl,  
quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl,  
benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl,  
20 benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl,  
pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-  
b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-  
benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl,  
carbazolyl, acridinyl, phenazinyl, phenothiazinyl,  
25 phenoxazinyl, or thianthrenyl, and said C<sub>1</sub>-C<sub>6</sub>  
heterocycloaliphatic group is piperidyl, pyrrolidinyl,  
imidazolidinyl, pyrazolidinyl, morpholinyl, or

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tetrahydrofuryl, (each of said C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, C<sub>6</sub>-C<sub>14</sub> aromatic, C<sub>1</sub>-C<sub>12</sub> heterocyclic aromatic and C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a halogen atom, a 10 trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonyl amide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a 25 thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a

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$C_1$ - $C_3$  alkyl group),

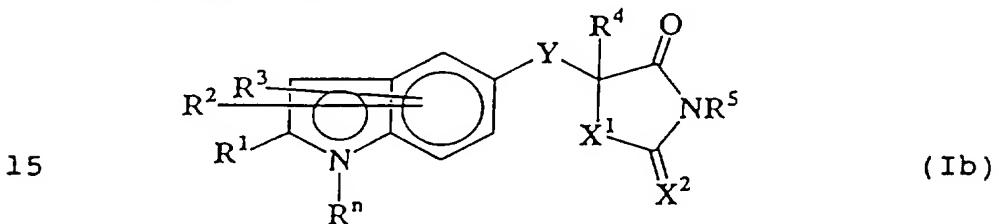
W is a divalent  $C_1$ - $C_6$  saturated or  $C_2$ - $C_6$  unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and  $C_1$ - $C_7$  alkyl groups, and

5 each of k and  $\ell$  is 0 or 1),

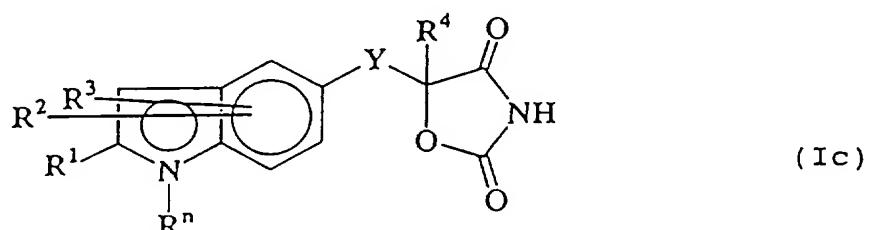
-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

(2) The indole type thiazolidine compound and its  
10 salt according to the above-mentioned (1), wherein the compound of the formula (Ia) is represented by the formula (Ib):



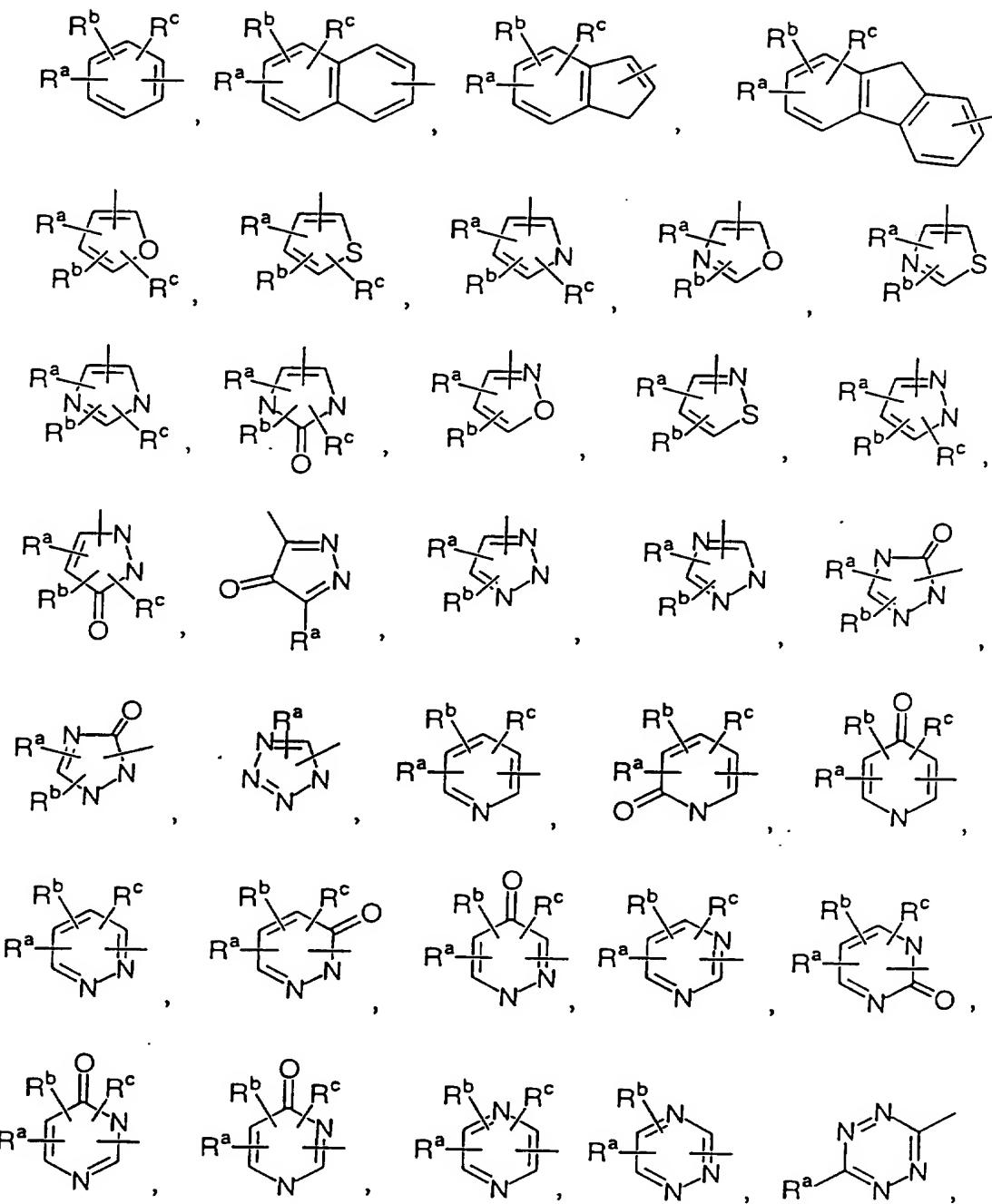
(3) The indole type thiazolidine compound and its salt according to the above-mentioned (2), wherein the compound of the formula (Ib) is represented by the  
20 following formula (Ic):



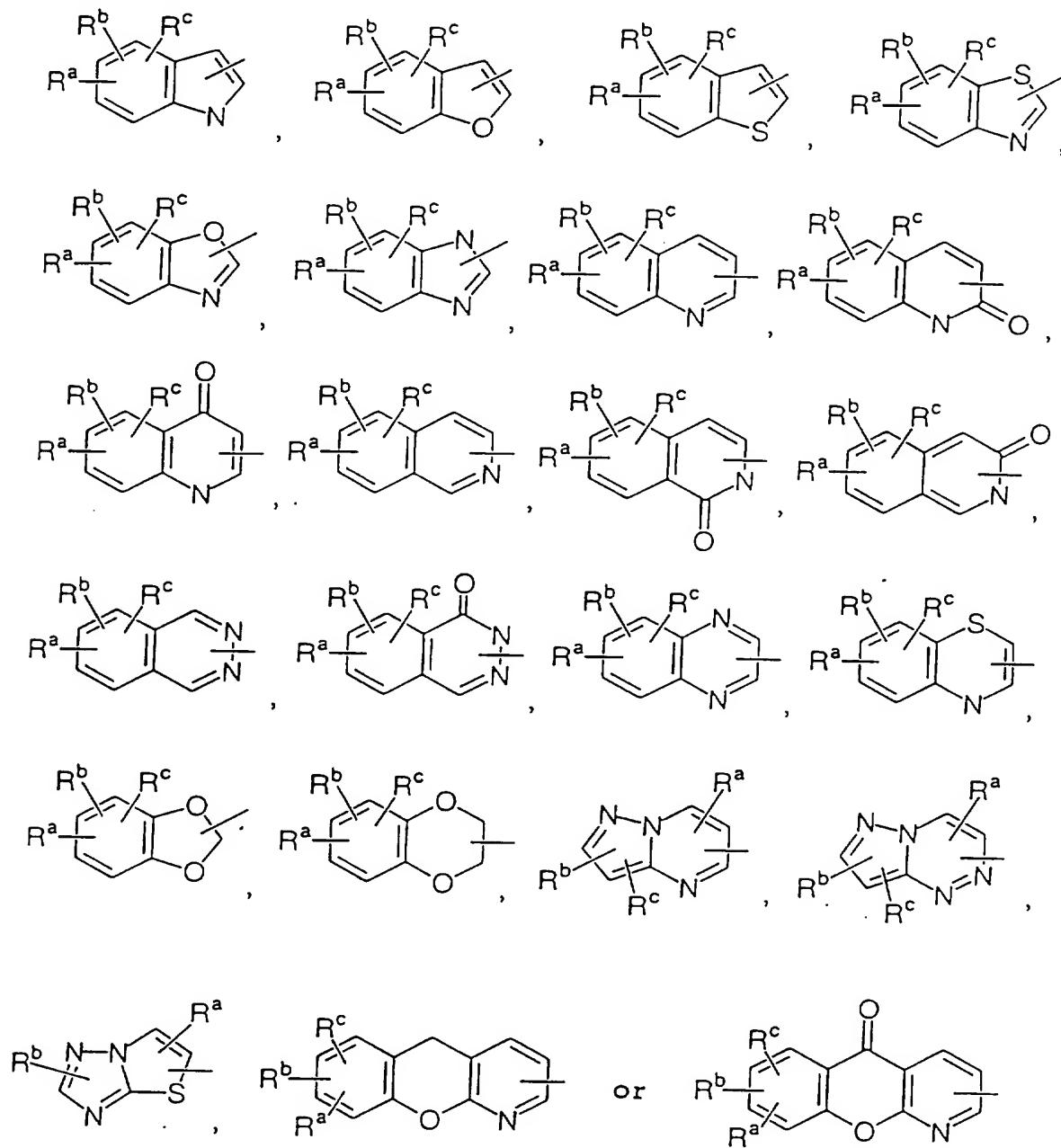
25 wherein  $R^1$  is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen

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atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group), W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups, when two W's are present, such W's 5 may be the same or different, and Z is



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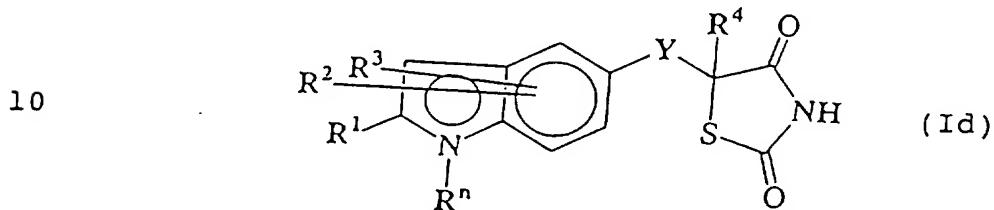
wherein each of R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group);

R<sup>2</sup> or R<sup>3</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a

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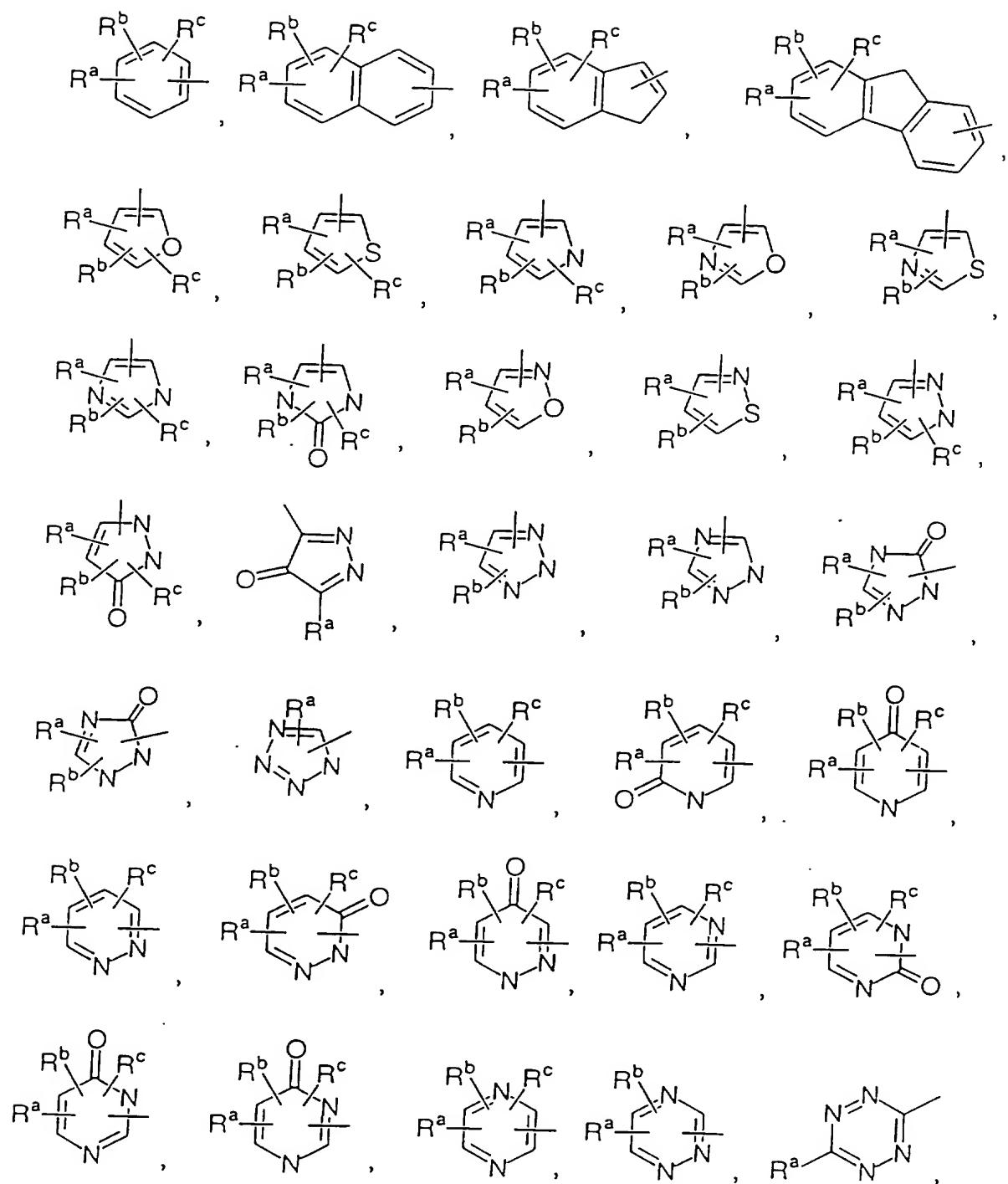
$C_3-C_6$  cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and  $R^5$  is a hydrogen atom.

(4) The indole type thiazolidine compound and its  
5 salt according to the above-mentioned (2), wherein the  
compound of the formula (Ib) is represented by the  
following formula (Id):

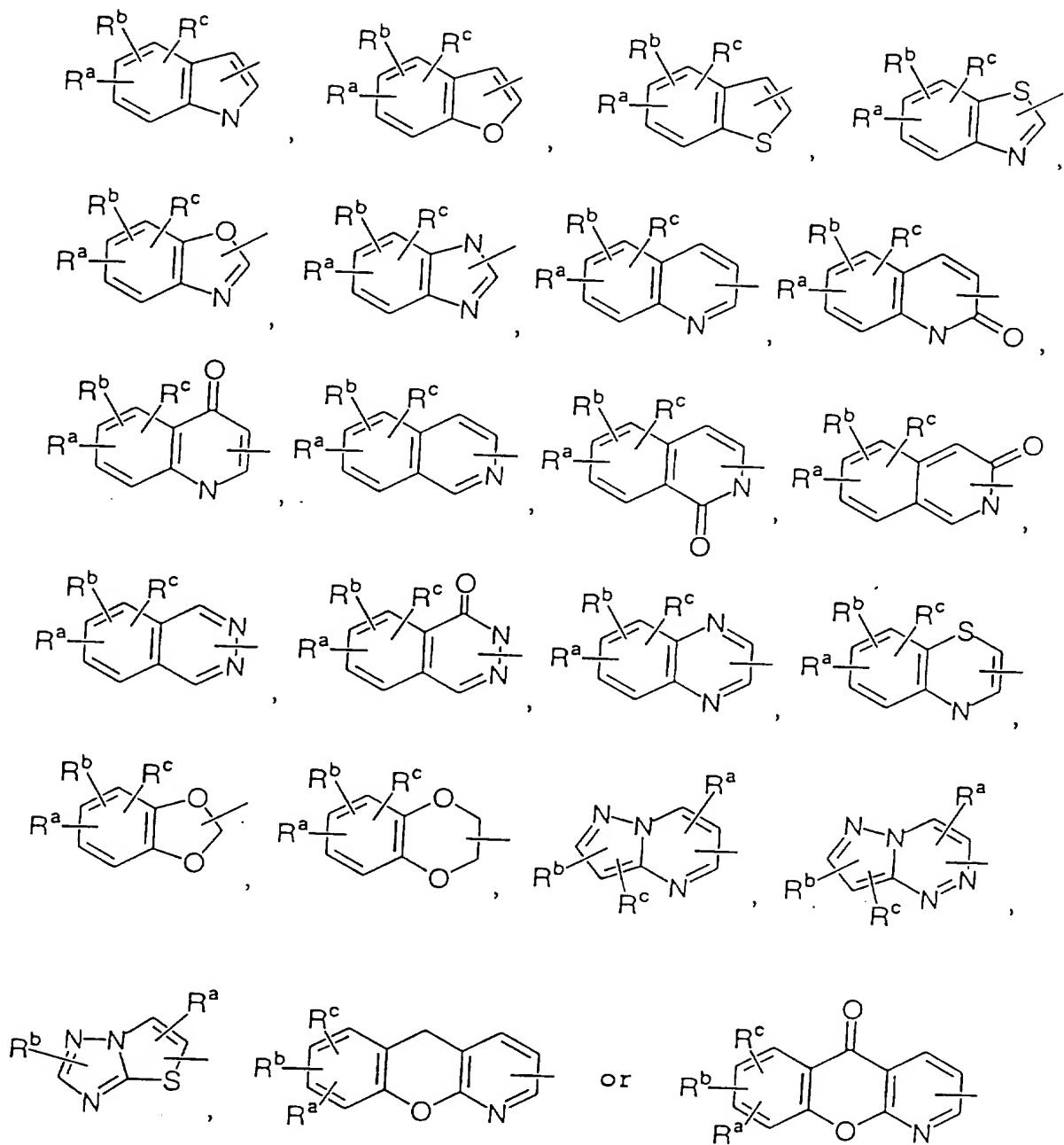


wherein  $R^1$  is a substituent at the 2-position of an  
indole ring, and is  $-W-Z$ ,  $-V-Z$ ,  $-W-V-Z$ ,  $-V-W-Z$  or  
15  $-W-V-W-Z$  ( $V$  is  $O$ ,  $S$ ,  $SO$ ,  $SO_2$  or  $NR^8$  ( $R^8$  is a hydrogen  
atom or a  $C_1-C_3$  alkyl group),  $W$  is a divalent  $C_1-C_6$   
saturated or  $C_2-C_6$  unsaturated hydrocarbon group which  
may be substituted with at most 3 of hydroxyl, oxo and  
 $C_1-C_7$  alkyl groups, when two  $W$ 's are present, such  $W$ 's  
20 may be the same or different, and  $Z$  is

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wherein each of R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group);

R<sup>2</sup> or R<sup>3</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a

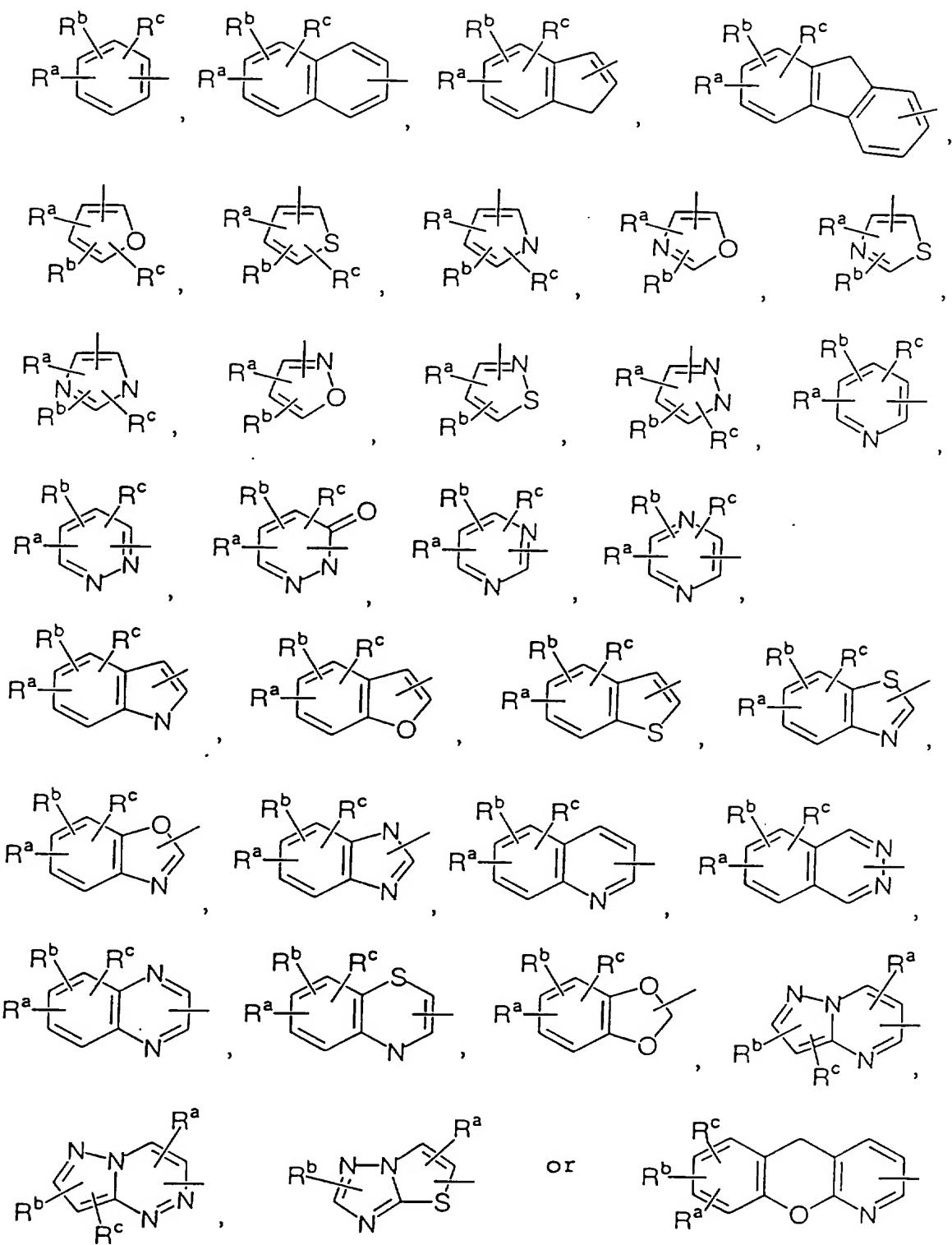
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$C_3-C_6$  cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and  $R^5$  is a hydrogen atom.

(5) The indole type thiazolidine compound and its  
5 salt according to the above-mentioned (4), wherein: Y is  $CR^6R^7$  ( $R^6$  is a hydrogen atom or a methyl group, and  $R^7$  is a hydrogen atom, or forms a bond together with  $R^4$ );

$R^1$  is a substituent at the 2-position of an indole ring, and is  $-W-Z$ ,  $-V-Z$ ,  $-W-V-Z$ ,  $-V-W-Z$  or  $-W-V-W-Z$  (V is 10 O, S,  $SO$ ,  $SO_2$  or  $NR^8$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group), W is a divalent  $C_1-C_6$  saturated or  $C_2-C_6$  unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and  $C_1-C_7$  alkyl groups (provided that the first carbon atom bonded to N is not 15 substituted with a hydroxyl group, and also provided that the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group) when two W's are present, such W's may be the same or different, and Z is

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wherein each R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonyl amide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group);

25 R<sup>4</sup> is a hydrogen atom or a methyl group, or forms a bond together with R<sup>7</sup>; and

R<sup>n</sup> is a substituent at the 1-position of an indole

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ring, and is a hydrogen atom, a C<sub>1</sub>-C<sub>3</sub> alkyl group, a cyclopropyl group, a C<sub>1</sub>-C<sub>2</sub> alkoxyethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, and a 5 trialkylsilyl group.

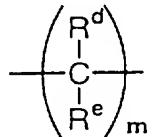
(6) The indole type thiazolidine compound and its salt according to the above-mentioned (5), wherein:

R<sup>1</sup> is -W-Z, wherein W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be 10 substituted with at most 2 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups.

(7) The indole type thiazolidine compound and its salt according to the above-mentioned (6), wherein:

R<sup>1</sup> is -W-Z, wherein W is

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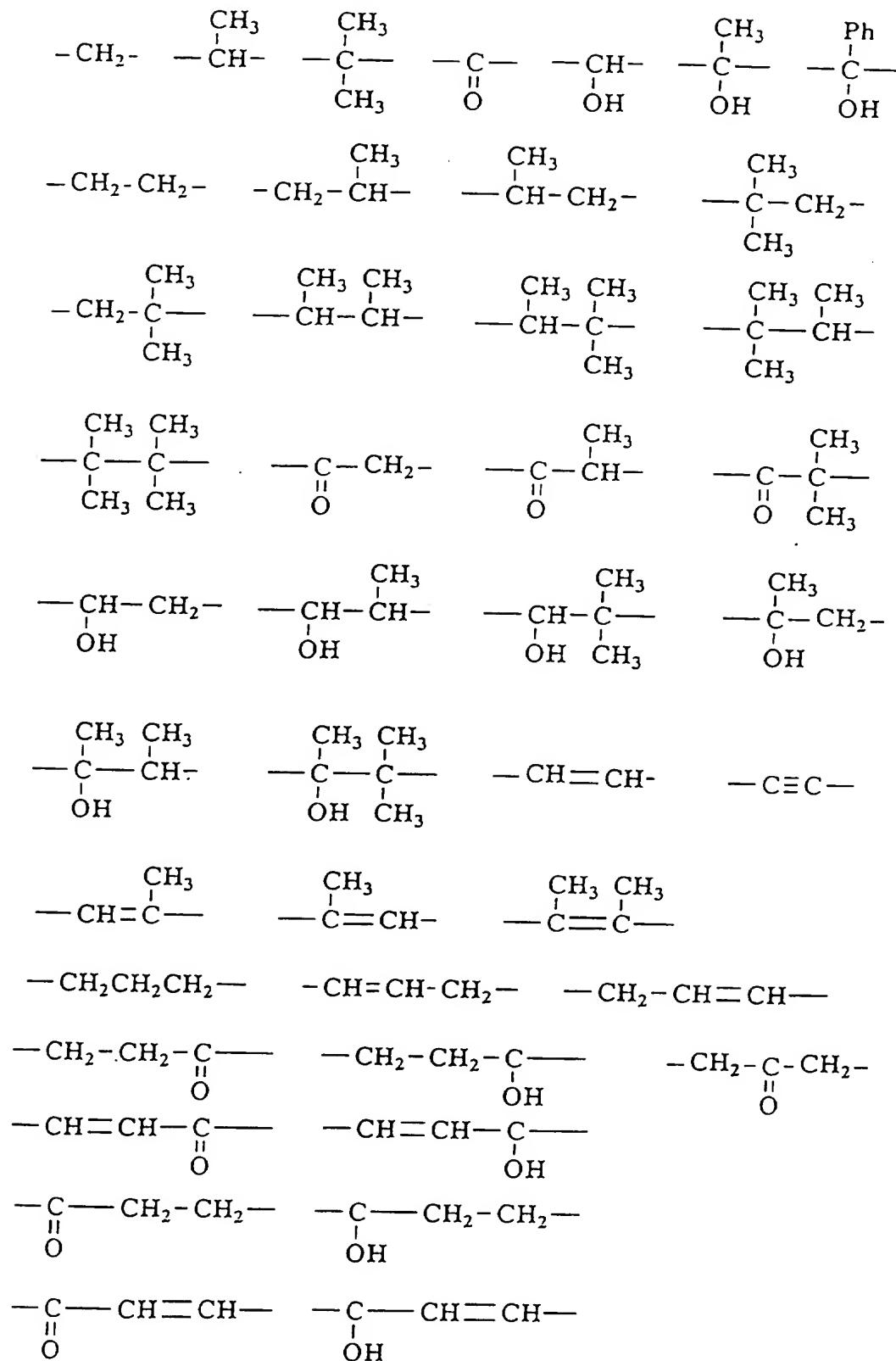


wherein m is from 1 to 5, and each of R<sup>d</sup> and R<sup>e</sup> is independently a hydrogen atom, a methyl group or a 20 hydroxyl group, or R<sup>d</sup> and R<sup>e</sup> together form an oxo group, or adjacent R<sup>d</sup>'s together form a double bond, or adjacent R<sup>d</sup>'s and R<sup>e</sup>'s together form a triple bond.

(8) The indole type thiazolidine compound and its salt according to the above-mentioned (7), wherein:

25 R<sup>1</sup> is -W-Z, wherein W is

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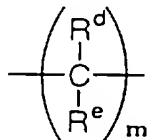
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(9) The indole type thiazolidine compound and its salt according to the above-mentioned (5), wherein:

R<sup>1</sup> is -V-Z, wherein V is S, SO or SO<sub>2</sub>.

(10) The indole type thiazolidine compound and its 5 salt according to the above-mentioned (5), wherein:

R<sup>1</sup> is -W-V-Z, wherein W is



10 wherein m is from 1 to 5, and each of R<sup>d</sup> and R<sup>e</sup> is independently a hydrogen atom, a methyl group or a hydroxyl group, or R<sup>d</sup> and R<sup>e</sup> together form an oxo group, or adjacent R<sup>d</sup>'s together form a double bond, or adjacent R<sup>d</sup>'s and R<sup>e</sup>'s together form a triple bond (provided that 15 R<sup>d</sup> and R<sup>e</sup> on the first carbon atom adjacent to N are not hydroxyl groups and also provided that R<sup>d</sup> and R<sup>e</sup> on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group),

V is NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group).

(11) The indole type thiazolidine compound and its salt according to the above-mentioned (10), wherein:

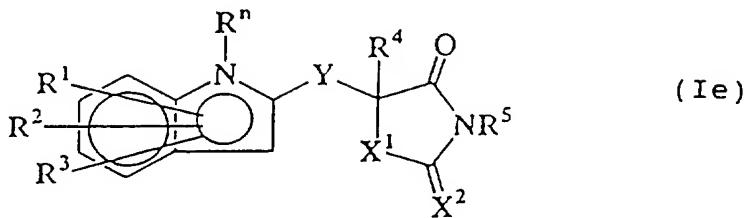
R<sup>1</sup> is -W-V-Z, wherein -W-V- is -CO-NR<sup>8</sup>- (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group).

25 (12) The indole type thiazolidine compound and its salt of the present invention, wherein the compound of the formula (I) is represented by the following formula

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(Ie):

5



wherein R<sup>1</sup> is a substituent at the 3-, 4-, 5-, 6- or 7-position of an indole ring, and is a C<sub>1</sub>-C<sub>10</sub> alkyl group, a C<sub>2</sub>-C<sub>10</sub> alkenyl group, a C<sub>2</sub>-C<sub>10</sub> alkynyl group, a C<sub>1</sub>-C<sub>10</sub> alkoxy group, a C<sub>2</sub>-C<sub>10</sub> alkenyloxy group, a C<sub>1</sub>-C<sub>10</sub> alkylthio group, a C<sub>1</sub>-C<sub>10</sub> monoalkylamino group or a di-C<sub>1</sub>-C<sub>10</sub> alkylamino group (each of said C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, C<sub>2</sub>-C<sub>10</sub> alkenyloxy, C<sub>1</sub>-C<sub>10</sub> alkylthio, C<sub>1</sub>-C<sub>10</sub> monoalkylamino and di-C<sub>1</sub>-C<sub>10</sub> alkylamino groups may be substituted with a hydroxyl group or a C<sub>1</sub>-C<sub>7</sub> alkyl group), or

-W<sub>k</sub>-V<sub>l</sub>-Z (among groups of Z as defined for the formula (I), said C<sub>3</sub>-C<sub>10</sub> cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, 20 bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl, said C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C<sub>6</sub>-C<sub>14</sub> aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C<sub>1</sub>-C<sub>12</sub> heterocyclic aromatic group is furyl, thieryl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl,

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oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl,  
pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl,  
pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl,  
tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl,  
5 benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl,  
benzothiazolyl, benzopyrazolyl, benzimidazolyl,  
benzotriazolyl, benzopyranyl, indolizinyl, purinyl,  
phthalazinyl, oxophthalazinyl, naphthyridinyl,  
quinoxaliny, quinazolinyl, cinnolinyl, benzodioxolyl,  
10 benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl,  
benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl,  
pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-  
b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-  
benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxythiinyl,  
15 carbazolyl, acridinyl, phenazinyl, phenothiazinyl,  
phenoxyazinyl, or thianthrenyl, and said C<sub>1</sub>-C<sub>6</sub>  
heterocycloaliphatic group is piperidyl, pyrrolidinyl,  
imidazolidinyl, pyrazolidinyl, morpholinyl, or  
tetrahydrofuran, (each of said C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub>,  
20 cycloalkenyl, C<sub>6</sub>-C<sub>14</sub> aromatic, C<sub>1</sub>-C<sub>12</sub> heterocyclic  
aromatic and C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic groups may have  
at most 5 substituents selected from the group consisting  
of a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub>  
cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl,  
25 cycloalkyl and cycloalkenyl groups may be substituted  
with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy  
group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a halogen atom, a

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trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonyl amide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group),

20 W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups, and each of k and ℓ is 0 or 1),

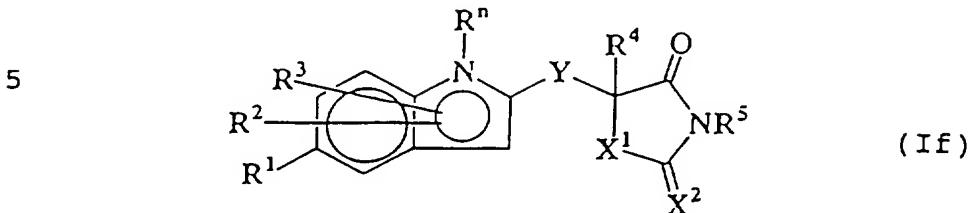
-V-W-Z (V, W and Z are as defined above), or

25 -W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

(13) The indole type thiazolidine compound and its

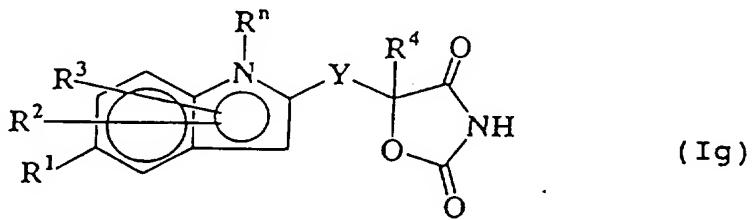
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salt according to the above-mentioned (12), wherein the compound of the formula (Ie) is represented by the formula (If):



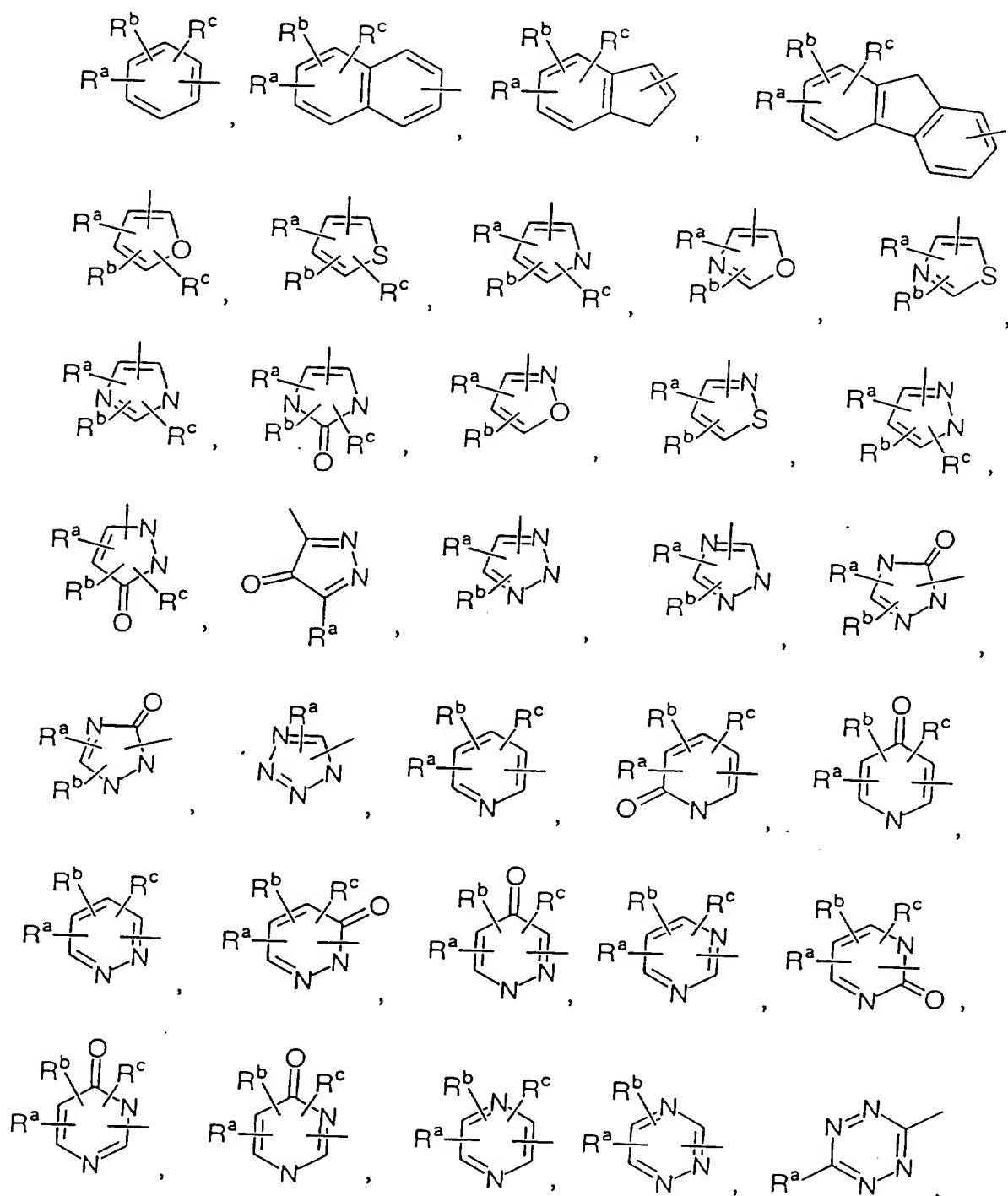
(14) The indole type thiazolidine compound and its salt according to the above-mentioned (13), wherein the 10 compound of the formula (If) is represented by the following formula (Ig):

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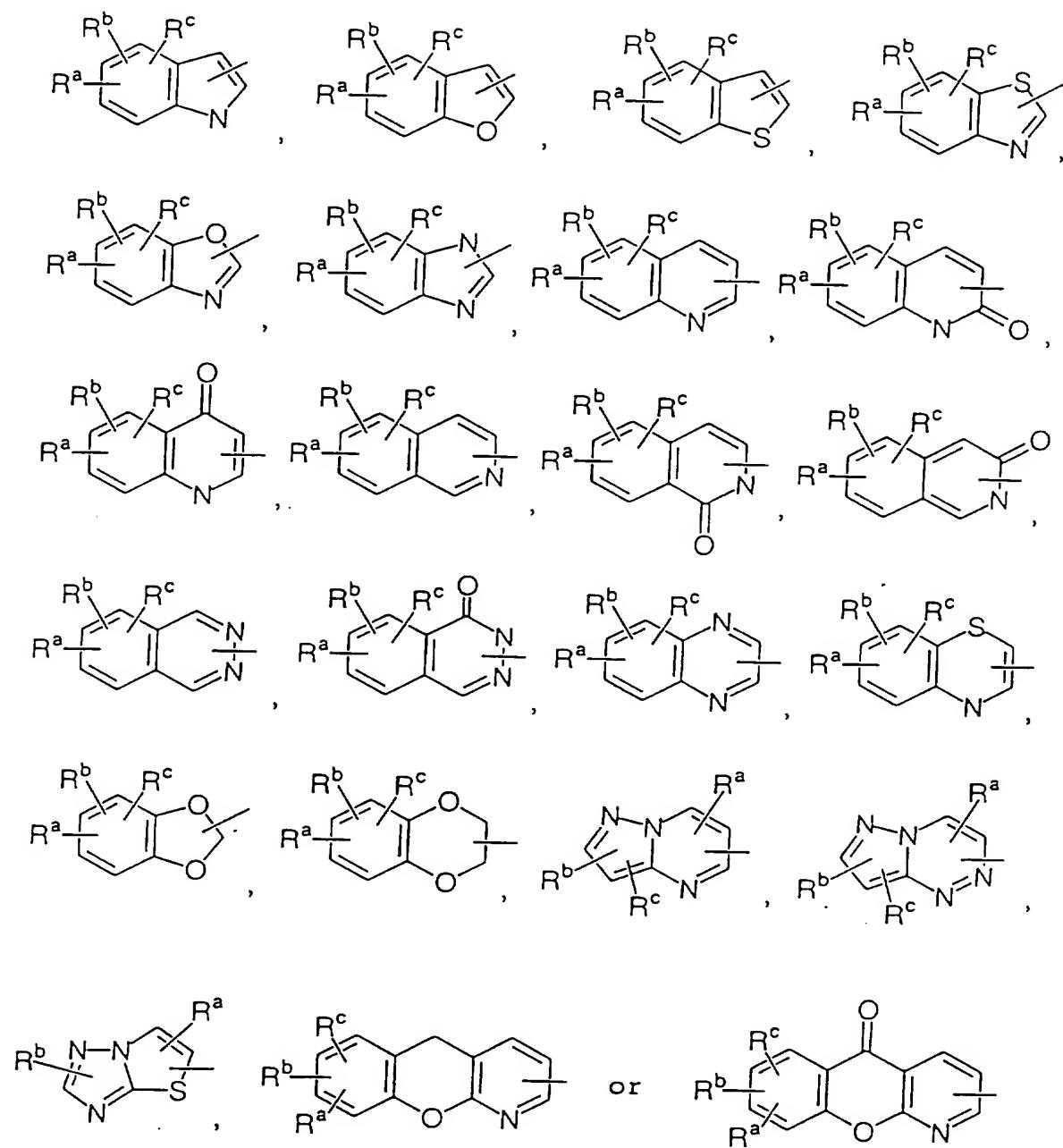


wherein R<sup>1</sup> is a substituent at the 5-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group), W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups, when two W's are present, such W's may be the same or different, and Z is

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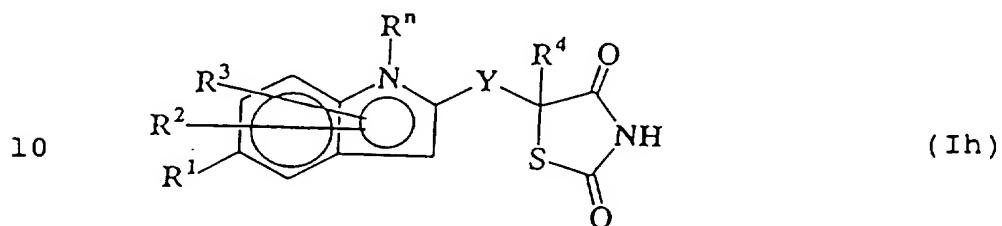
wherein each of R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group);

R<sup>2</sup> or R<sup>3</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a

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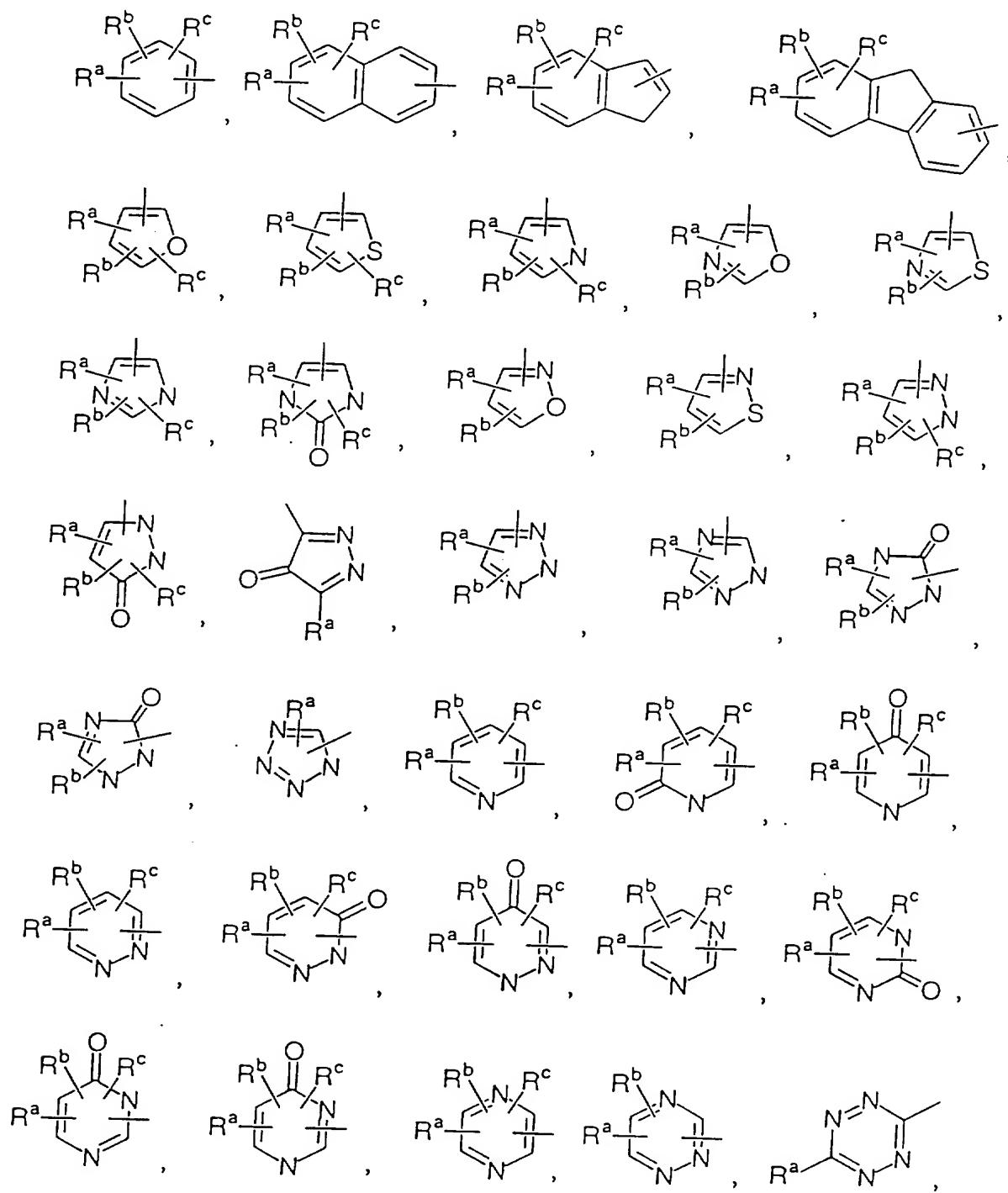
$C_3-C_6$  cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and  $R^5$  is a hydrogen atom.

(15) The indole type thiazolidine compound and its  
5 salt according to the above-mentioned (13), wherein the compound of the formula (If) is represented by the following formula (Ih):

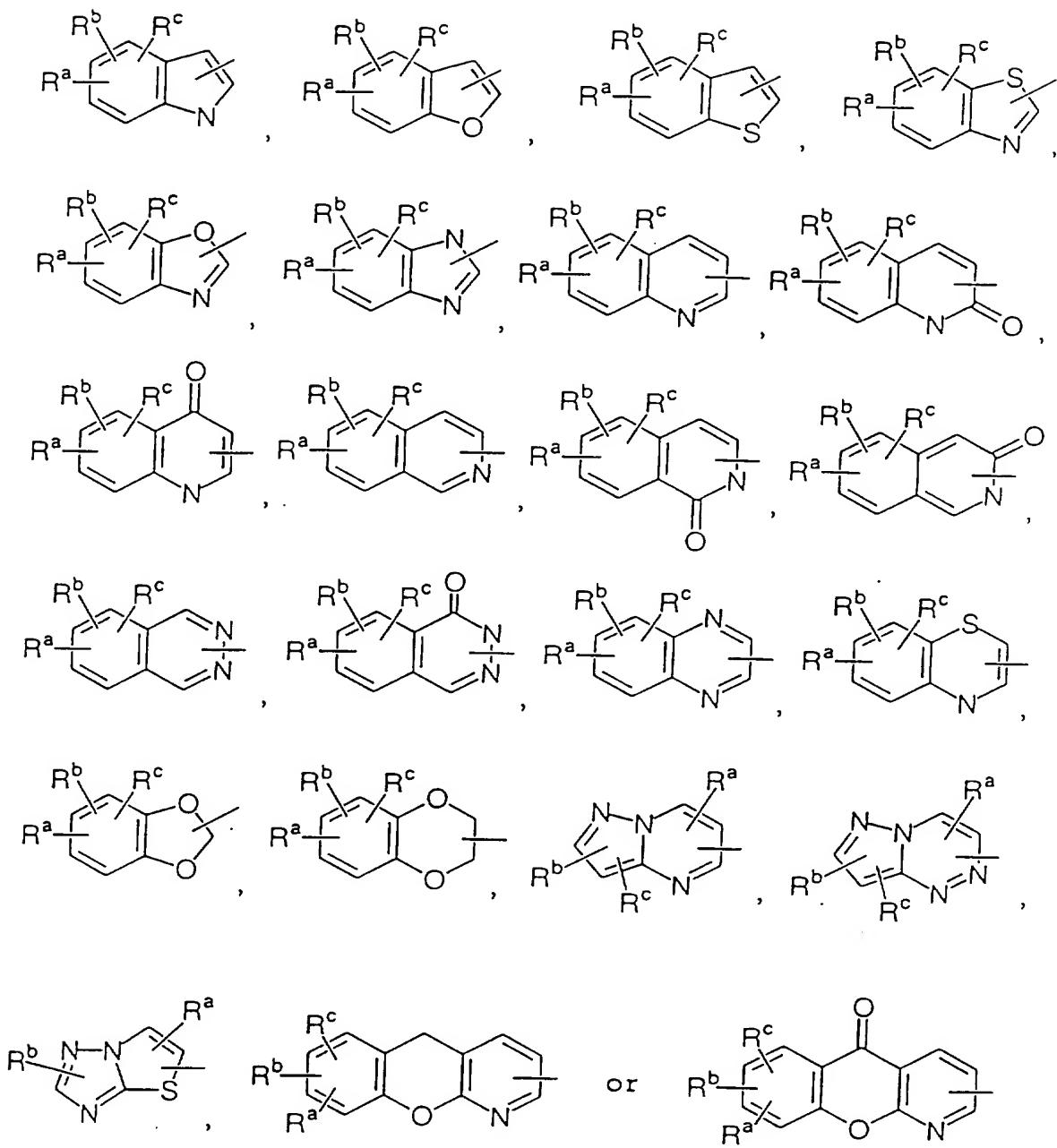


wherein  $R^1$  is  $-V-W-Z$ ,  $-W-Z$ ,  $-V-W-V-W-Z$ ,  $-W-V-W-Z$ ,  $-V-W-V-Z$  or  $-W-V-Z$  ( $V$  is O, S or  $NR^8$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group),  $W$  is a divalent  $C_1-C_6$  saturated or  $C_2-C_6$  unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and  $C_1-C_7$  alkyl groups, when two  $V$ 's or  $W$ 's are present, such  $V$ 's or  $W$ 's may be the same or different, and  $Z$  is

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wherein each of R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonyl amide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group;

R<sup>2</sup> or R<sup>3</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a

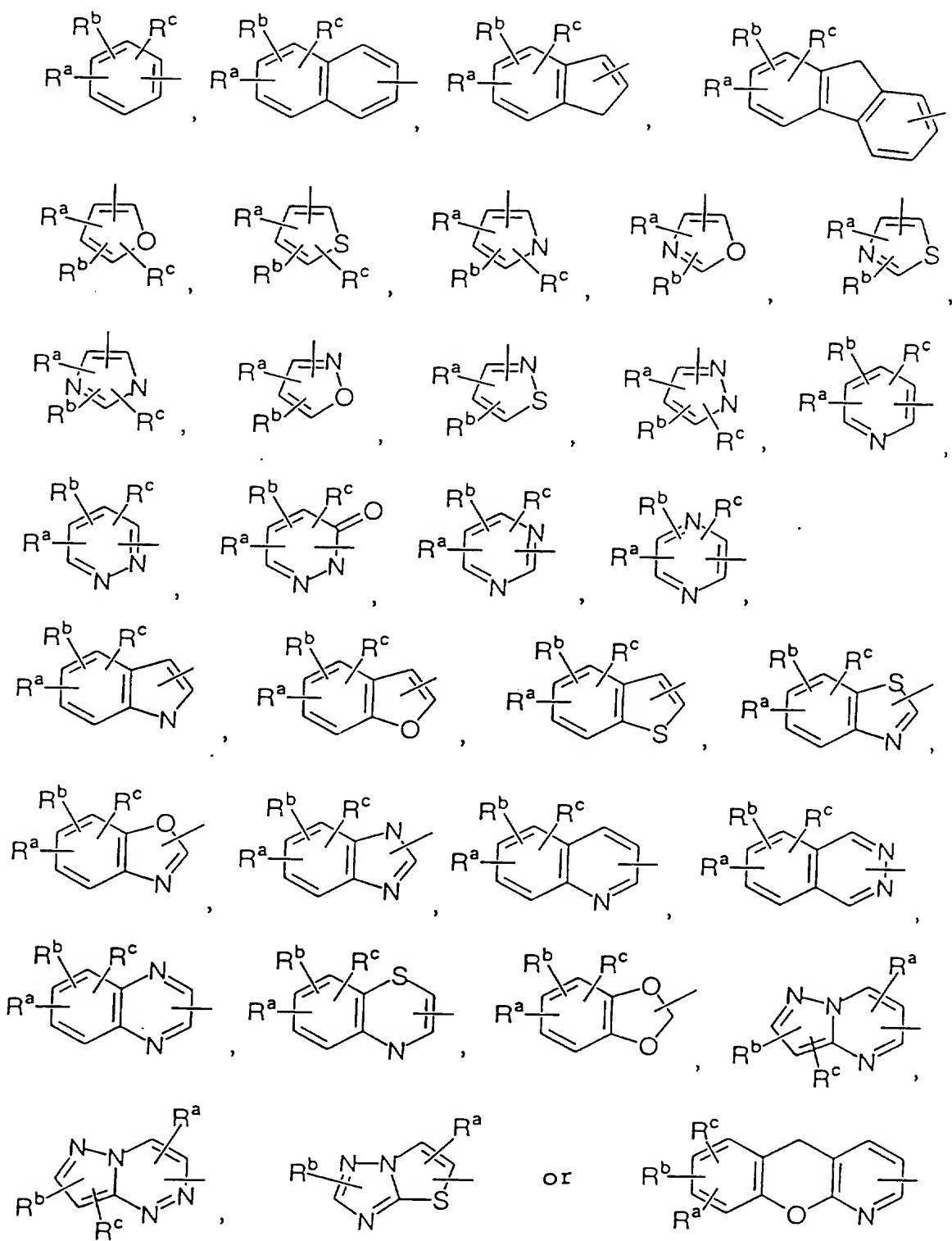
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$C_3-C_6$  cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and  $R^5$  is a hydrogen atom.

(16) The indole type thiazolidine compound and its 5 salt according to the above-mentioned (15), wherein: Y is  $CR^6R^7$  ( $R^6$  is a hydrogen atom or a methyl group, and  $R^7$  is a hydrogen atom, or forms a bond together with  $R^4$ );

10  $R^1$  is a substituent at the 5-position of an indole ring, and is  $-W-Z$ ,  $-V-Z$ ,  $-W-V-Z$ ,  $-V-W-Z$  or  $-W-V-W-Z$  (V is O, S,  $SO_2$  or  $NR^8$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group), W is a divalent  $C_1-C_6$  saturated or  $C_2-C_6$  unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and  $C_1-C_7$  alkyl groups (provided that the first carbon atom bonded to N is not 15 substituted with a hydroxyl group, and also provided that the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group), when two W's are present, such W's may be the same or different, and Z is

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wherein each  $R^a$  and  $R^b$  is independently a hydrogen atom, a  $C_1$ - $C_7$  alkyl group, a  $C_3$ - $C_7$  cycloalkyl group, a  $C_3$ - $C_7$  cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a  $C_1$ - $C_7$  alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a  $C_1$ - $C_3$  alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri- $C_1$ - $C_7$ -alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a  $C_1$ - $C_7$  alkyl group, a  $C_3$ - $C_7$  cycloalkyl group, a  $C_1$ - $C_3$  alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and  $R^c$  is a hydrogen atom, a  $C_1$ - $C_7$  alkyl group, a  $C_3$ - $C_7$  cycloalkyl group or a hydroxymethyl group);

$R^4$  is a hydrogen atom or a methyl group, or forms a bond together with  $R^7$ ; and

$R^n$  is a substituent at the 1-position of an indole

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ring, and is a hydrogen atom, a C<sub>1</sub>-C<sub>3</sub> alkyl group, a cyclopropyl group, a C<sub>1</sub>-C<sub>2</sub> alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, and a 5 trialkylsilyl group.

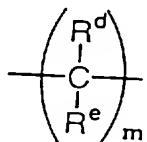
(17) The indole type thiazolidine compound and its salt according to the above-mentioned (16), wherein:

R<sup>1</sup> is -W-Z, wherein W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be 10 substituted with at most 2 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups.

(18) The indole type thiazolidine compound and its salt according to the above-mentioned (17), wherein:

R<sup>1</sup> is -W-Z, wherein W is

15

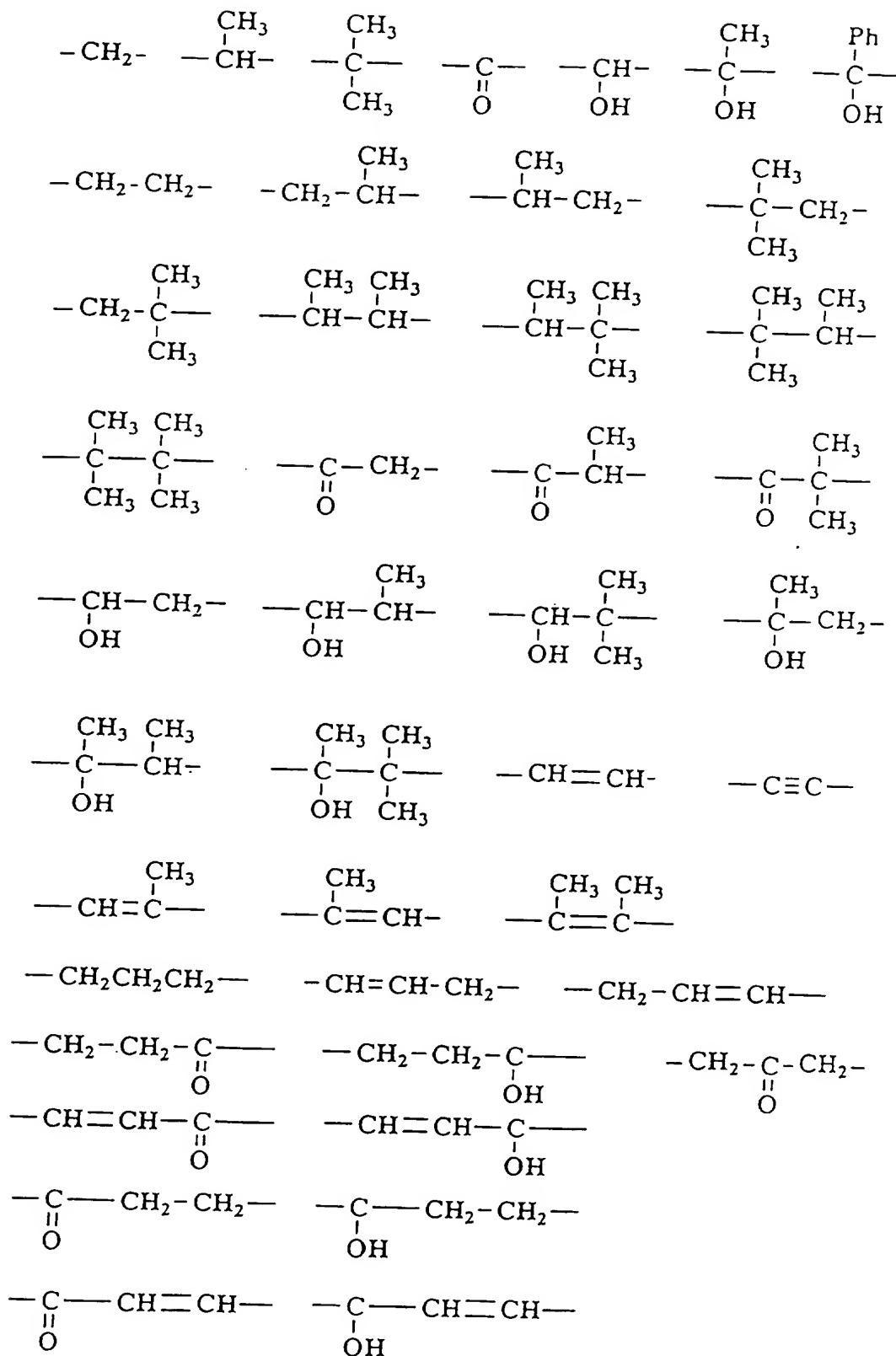


wherein m is from 1 to 5, and each of R<sup>d</sup> and R<sup>e</sup> is independently a hydrogen atom, a methyl group or a 20 hydroxyl group, or R<sup>d</sup> and R<sup>e</sup> together form an oxo group, or adjacent R<sup>d</sup>'s together form a double bond, or adjacent R<sup>d</sup>'s and R<sup>e</sup>'s together form a triple bond.

(19) The indole type thiazolidine compound and its salt according to the above-mentioned (18), wherein:

25 R<sup>1</sup> is -W-Z, wherein W is

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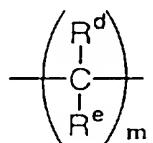
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(20) The indole type thiazolidine compound and its salt according to the above-mentioned (16), wherein:

$R^1$  is  $-V-Z$ , wherein  $V$  is  $S$ ,  $SO$  or  $SO_2$ .

(21) The indole type thiazolidine compound and its salt according to the above-mentioned (16), wherein:

$R^1$  is  $-W-V-Z$ , wherein  $W$  is



wherein  $m$  is from 1 to 5, and each of  $R^d$  and  $R^e$  is independently a hydrogen atom, a methyl group or a hydroxyl group, or  $R^d$  and  $R^e$  together form an oxo group, or adjacent  $R^d$ 's together form a double bond, or adjacent  $R^d$ 's and  $R^e$ 's together form a triple bond (provided that  $R^d$  and  $R^e$  on the first carbon atom adjacent to N are not a hydroxyl group, and also provided that  $R^d$  and  $R^e$  on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group), and

$V$  is  $NR^8$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group).

(22) The indole type thiazolidine compound and its salt according to the above-mentioned (21), wherein:

$R^1$  is  $-W-V-Z$ , wherein  $-W-V-$  is  $-CO-NR^8-$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group).

(23) The indole type thiazolidine compound and its salt according to the above-mentioned (8), (9), (11), (19), (20) or (21), wherein:

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Y is  $-\text{CH}_2-$ ; and

$\text{R}^4$  is a hydrogen atom.

(24) The indole type thiazolidine compound and its salt according to the above-mentioned (8), (9), (11), 5 (19), (20) or (21), wherein: Y is  $\text{CHR}^7$  ( $\text{R}^7$  forms a bond together with  $\text{R}^4$ ), and  $\text{R}^4$  forms a bond together with  $\text{R}^7$ .

The compound of the above formula (I) of the present invention has acidic hydrogen on a thiazolidine ring or on an oxazolidine ring. Further, when substituent Z is a 10 heterocyclic aromatic group or a heterocyclic aliphatic group, it sometimes has a basic nitrogen. Such a compound may be converted to a pharmaceutically acceptable non-toxic salt with an appropriate base or acid, if desired. The compound of the formula (I) can be 15 used for the purpose of the present invention either in the free form or in the form of a pharmaceutically acceptable salt. Examples of the basic salt include an alkali metal salt (lithium salt, sodium salt, potassium salt and the like), an alkali earth metal salt (calcium 20 salt, magnesium salt and the like), an aluminum salt, an ammonium salt which may be unsubstituted or substituted with a methyl, ethyl or benzyl group, an organic amine salt (methylamine salt, ethylamine salt, dimethylamine salt, diethylamine salt, trimethylamine salt, 25 triethylamine salt, cyclohexylamine salt, ethylenediamine salt, bicyclohexylamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, piperazine

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salt, dibenzylpiperidine salt, dehydroabietilamine salt, N,N'-bisdehydroabietilamine salt, benzathine(N,N'-dibenzylethylenediamine) salt, glucamine salt, meglumine(N-methylglucamine) salt, benetamine(N-5 benzylphenethylamine)salt, trometamine(2-amino-2-hydroxymethyl-1,3-propanediol)salt, choline salt, procaine salt), a basic amino acid salt (lysine salt, ornithine salt, arginine salt and the like), a pyridine salt, a collidine salt, a quinoline salt, and the like.

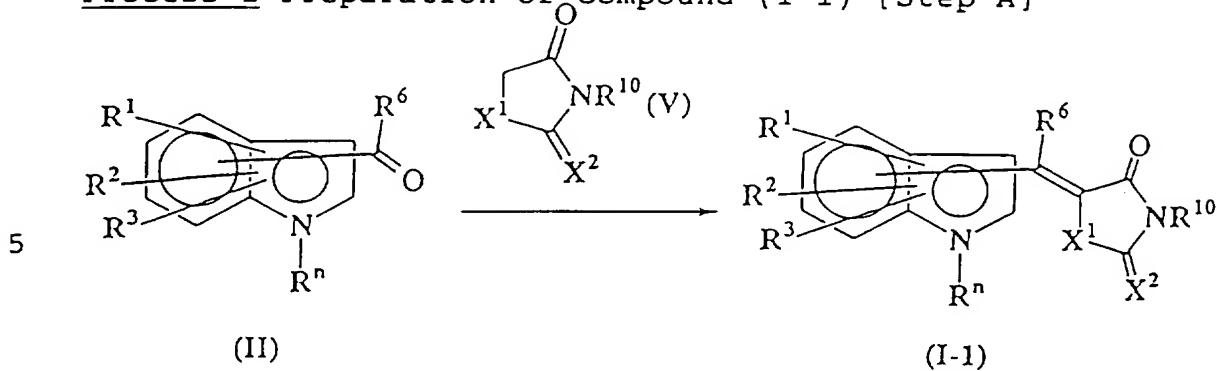
10 Examples of an acid-addition salt include a mineral acid salt (hydrochloride, hydrobromide, sulfate, hydrogensulfate, nitrate, phosphate, hydrogenphosphate, dihydrogenphosphate and the like), an organic acid salt (formate, acetate, propionate, succinate, malonate, 15 oxalate, maleate, fumarate, malate, citrate, tartrate, lactate, glutamate, asparate, picrate, carbonate and the like), a sulfonic acid salt (methanesulfonate, benzenesulfonate, toluenesulfonate and the like), and the like. Each of these salts can be prepared by a known 20 method.

The compound having the formula (I), i.e. indole type thiazolidines, can be prepared by the following synthetic methods.

A reaction solvent used in the preparation is stable 25 under the reaction conditions, and is preferably so inert as not to inhibit the reaction. Examples of the reaction solvent include water, alcohols (such as methanol,

ethanol, propanol, butanol and octanol), cellosolves (such as methoxyethanol and ethoxyethanol), aprotic polar organic solvents (such as dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetramethylurea, 5 sulfolane and N,N-dimethylimidazolidinone), ethers (such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane), aliphatic hydrocarbons (such as pentane, n-hexane, c-hexane, octane, decaline and petroleum ether), aromatic hydrocarbons (such as benzene, chlorobenzene, 10 nitrobenzene, toluene, xylene and tetralin), halogenated hydrocarbons (such as chloroform, dichloromethane and dichloroethane), ketones (such as acetone, methyl ethyl ketone and methyl butyl ketone), lower aliphatic acid esters (such as methyl acetate, ethyl acetate and methyl 15 propionate), alkoxy alkanes (such as dimethoxyethane and diethoxyethane), acetonitrile, and the like. These solvents are optionally selected depending on the reactivity of the aimed reaction, and are respectively used alone or in a mixture. In some cases, there are 20 used as an anhydrous solvent by using a dehydrating agent or a drying agent. The above-mentioned solvents are merely examples which can be used in the reaction of the present invention, and the present invention is not limited to these conditions.

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Process 1 Preparation of Compound (I-1) [Step A]

(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^6$ ,  $R^n$ ,  $X^1$  and  $X^2$  are as defined above, and  $R^{10}$  is a hydrogen atom or a protecting group of amide (such as Tr: trityl)).

10

A compound wherein  $R^4$  and  $R^7$  are bonded together in the formula (I), i.e. a compound of the formula (I-1), can be obtained by dehydration-condensation of a compound of the formula (II) and a compound of the formula (V).

15 The compound of the formula (II) is a well known compound or can be synthesized by the method disclosed in Japanese Unexamined Patent Publication No. 271288/1991, Japanese Unexamined Patent Publication No. 277660/1988, Japanese Unexamined Patent Publication No. 71321/1975 or Japanese  
20 Examined patent Publication No. 34986/1974. The compound of the formula (V) is a well known compound or can be synthesized by the method disclosed in "J. Prakt. Chem." (vol. 2, p. 253, 1909), "J. Prakt. Chem." (vol. 3, p. 45, 1919), "Chem. Ber." (vol. 118, p. 774, 1985), and German  
25 Laid Open Patent Publication No. DE-3045059. The compound of the formula (V) wherein  $R^{10}$  is hydrogen, can be used in this reaction after displacing its acidic

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hydrogen at the 3-position of thiazolidine or oxazolidine with an appropriate substituent (such as TR: trityl) by a well known method.

This reaction is conducted usually in an appropriate 5 organic solvent in the presence of base or acid.

Examples of such a solvent include alcohols, cellosolves, aprotic polar organic solvents, ethers, aromatic hydrocarbons, halogenated hydrocarbons, alkoxyalkanes and acetonitrile.

10 Examples of the base and the acid include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine),

15 Acid Capture H: 3,4-dihydro-2H-pyrid[1,2-a]pyrimidin-2-one, Acid Capture 9M: 9-methyl-3,4-dihydro-2H-pyrid[1,2-a]pyrimidin-2-one, and the like, or metal alkoxides (such as sodium methoxide, sodium ethoxide, lithium isopropoxide and potassium t-butoxide), inorganic alkali

20 metal salts (such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydride, potassium hydride, calcium hydride, sodium acetate and potassium acetate), organic acids (such as acetic acid, trichloroacetic acid

25 and trifluoroacetic acid), inorganic acids (such as phosphoric acid), and the like. These materials are selected appropriately depending on the reactivity of the

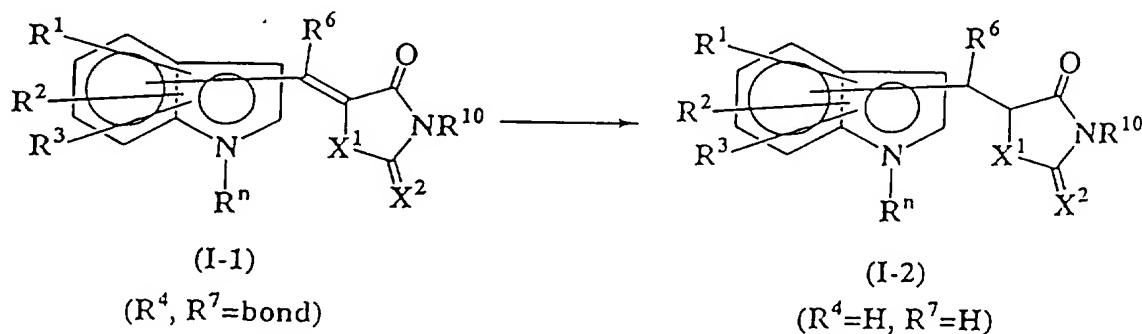
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aimed reaction.

This reaction can be accelerated by removing water formed during the reaction out of the system by using an appropriate dehydrating agent such as molecular sieves 5 and anhydrous sodium sulfate or by azeotropic distillation using Dean-Stark tube.

This reaction is conducted usually at a temperature ranging from 0°C to a boiling point of a solvent used, preferably from 20°C to 120°C, for from 0.5 to 30 hours.

10 Process 2 Preparation of Compound (I-2) [Step B]



(wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup>, R<sup>10</sup>, R<sup>n</sup>, X<sup>1</sup> and X<sup>2</sup> are as defined above).

20 A compound of the formula (I-1) (R<sup>4</sup> and R<sup>7</sup> together form a bond) obtained by the above method can be converted into a compound of the formula (I-2) (R<sup>4</sup> and R<sup>7</sup>=H) in accordance with an appropriate reduction method, for example by catalytically hydrogenating in the presence of an appropriate catalyst, or by using an appropriate metal-hydrogen complex compound, or by 25 reducing a double bond connecting an indole ring with a

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thiazolidine or oxazolidine ring in a lower alcohol such as methanol by magnesium or sodium amalgam.

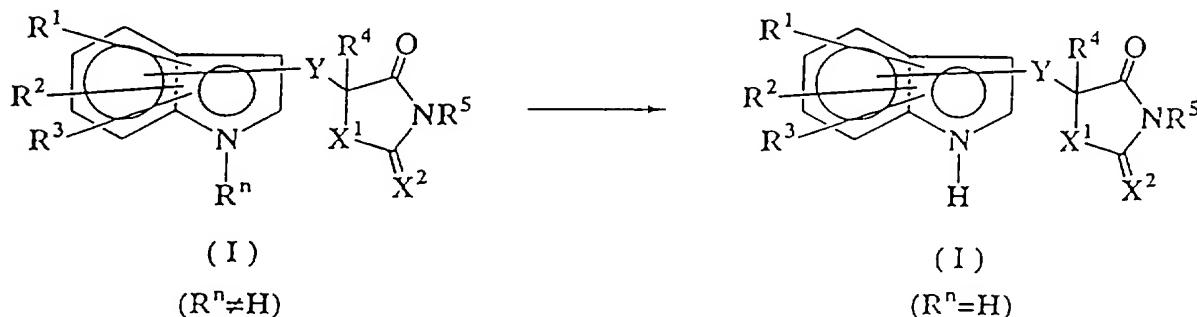
The reduction reaction by catalytic hydrogenation is conducted usually in a solvent such as water, alcohols, 5 cellosolves, aprotic polar organic solvents, ethers, alkoxyalkanes, lower aliphatic acid esters or lower aliphatic acids, preferably water, methanol, ethanol, methoxyethanol, dimethylformamide, dimethylacetamide, tetrahydrofuran, dioxane, dimethoxyethane, ethylacetate 10 or acetic acid. The solvent may be used alone or in a mixture. Examples of the catalyst used in this reaction include Raney nickel, palladium black, palladium carbon, ruthenium carbon, platinum oxide and the like. This reaction proceeds usually at normal temperature and a 15 atmospheric pressure but it is preferable for accelerating the procedure of the reaction to optionally employ an elevated temperature and a higher pressure.

In the case of the reduction reaction using a metal-hydrogen complex compound, a reaction is conducted in 20 water or an appropriate organic solvent at a temperature of from 0°C to 150°C, preferably from 0°C to 30°C, and examples of the metal-hydrogen complex compound include sodium borohydride, potassium borohydride, lithium borohydride, sodium cyanoborohydride, potassium tri-s- 25 butylborohydride, potassium triethylborohydride, lithium triethylborohydride, sodium triethylborohydride, tetramethylammonium borohydride, tetra-n-butylammonium

borohydride, tetra-n-butylammonium cyanoborohydride, sodium triacetoxyborohydride, tetra-n-butylammonium triacetoxyborohydride, lithium thexylborohydride, potassium triphenylborohydride, sodium 5 trimethoxyborohydride, rhodium borohydride, tetraethylammonium borohydride, methyltrioctylammonium boronydride, calcium borohydride bis(tetrahydrofuran), lithium dimethylborohydride, zinc borohydride and the like. Also, in this reduction, an undesired side 10 reaction can be inhibited by adding a Co reagent such as  $\text{CoCl}_2$ ,  $\text{CoCl}_3$  and  $\text{Co}(\text{OAc})_2$  in the presence of a ligand such as dimethyl glyoxime, 2,2'-dipyridyl and 1,10-phenanthroline (see WO 93/13095).

In the case of the reduction using an amalgam, the 15 reaction is conducted in a solvent such as alcohols, preferably ethanol or ethanol at a temperature of from -20°C to a boiling point of a solvent used, preferably from 0°C to 50°C. Also, the reduction method by magnesium/methanol can be employed, as described in "J. 20 Org. Chem.", vol. 40, P 127 (1975).

Process 3 Preparation of Compound (I) (Displacement of substituent  $\text{R}^n$ ) [Step C]



(wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, X<sup>1</sup>, X<sup>2</sup> and Y are as defined above, R<sup>n</sup> is a substituent (other than a hydrogen atom) at the 1-position of an indole ring).

Among the compounds of the formula (I), the R<sup>n</sup> substituent other than a hydrogen atom at the 1-position of an indole ring can be converted to a hydrogen atom by a well known appropriate method. The following reaction conditions can be employed depending on the type of the substituent R<sup>n</sup>.

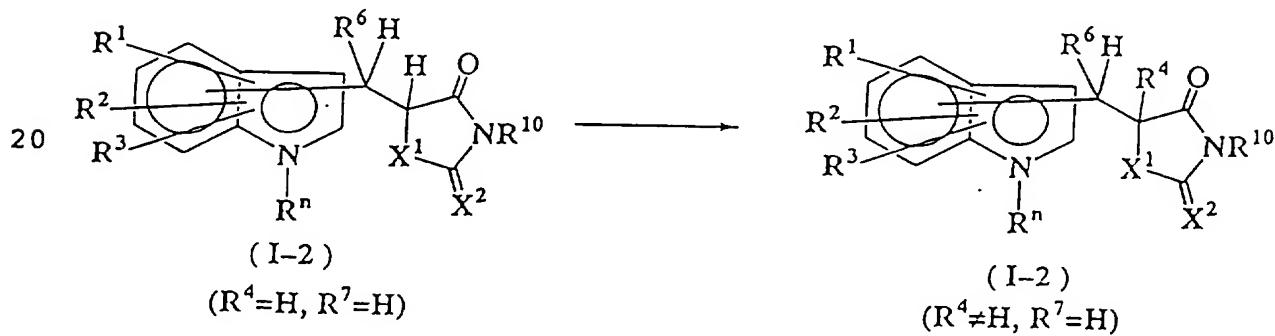
The displacement of the R<sup>n</sup> substituent can be conducted by heat-refluxing for 1 to 12 hours in a mixture solution of sodium hydroxide aqueous solution/ethanol when R<sup>n</sup> is a benzenesulfonyl group, a p-toluenesulfonyl group or a p-methoxybenzenesulfonyl group; by catalytically reducing in the presence of palladium carbon, lithium aluminum hydride or Raney nickel in methanol, ethyl acetate or tetrahydrofuran when R<sup>n</sup> is a methoxy group, a methoxymethoxy group, a methoxyethoxy group or a benzyloxymethoxy group; by stirring at room temperature in trifluoroacetic acid, a mixture solution of sodium hydroxide/methanol or a mixture solution of hydrochloric acid aqueous solution/methanol when R<sup>n</sup> is a tertiary butylamino carbonyl group or a tertiary butoxy carbonyl group; by using tetra-n-butylammonium fluoride or cesium fluoride in tetrahydrofuran at room temperature when R<sup>n</sup> is a trimethylsilyl group, a tertiary butyldimethylsilyl

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group, a tertiary butyldiphenylsilyl group or a triisopropylsilyl group; by stirring at room temperature in a mixture solution of sodium hydroxide aqueous solution/ethanol when  $R^n$  is an acetyl group or a 5 trifluoroacetyl group; by using tetrabutylammonium fluoride or a cesium fluoride at room temperature in tetrahydrofuran when  $R^n$  is a trimethylsilylethyoxyethyl group; by using lithium bromide and boron trifluoride/ether complex and acetic anhydride when  $R^n$  is 10 a methoxymethyl group; by using sodium methoxide or sodium borohydride in methanol at room temperature when  $R^n$  is a dimethylaminomethyl group; or by heating at 80°C to 200°C and decarboxylating when  $R^n$  is a carboxyl group, thus converting the substituent at the 1-position to a 15 hydrogen atom.

Process 4 Displacement of  $R^4$  substituent of Compound

(I-2) [Step D]



25 (wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$ ,  $R^{10}$ ,  $X^1$  and  $X^2$  are as defined above).

A compound of the formula (I-2) ( $R^4$ ,  $R^7=H$ ) can be

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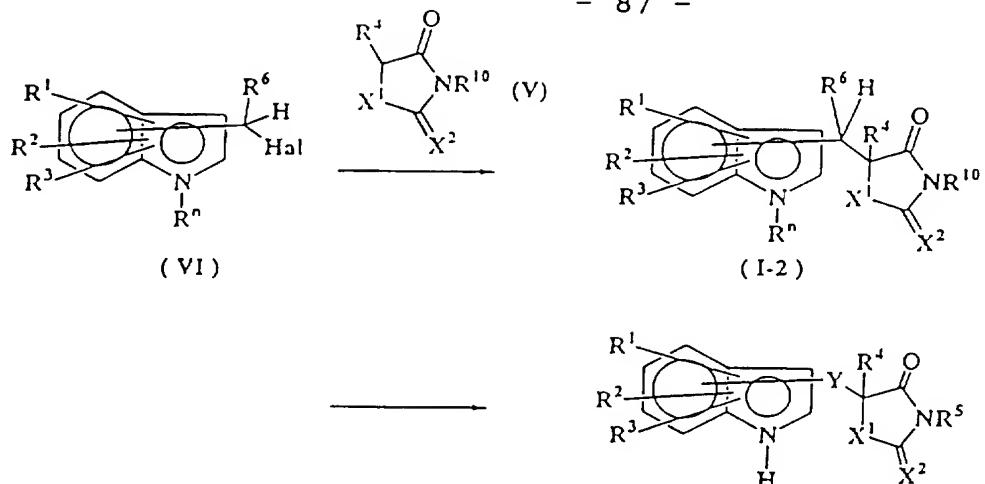
converted into a compound of the formula (I-2) ( $R^4 \neq H$ ,  $R^7 = H$ ) in accordance with a well known method by alkylating hydrogen at the 5-position of a thiazolidine or oxazolidine ring with an appropriate alkylating agent 5 (such as alkylhalides including methyliodide and ethyliodide, alkylsulfates including dimethylsulfate and diethylsulfate, or aliphatic or aromatic sulfonic acid esters including methyltosylate and methylmesylate).

This reaction is conducted usually in the presence of 10 a base in an appropriate organic solvent. Examples of the solvent used include aprotic polar organic solvents, ethers, and alkoxy alkanes, preferably tetrahydrofuran and dimethoxy ethane. Examples of the base include alkali metal amides (such as LDA: lithium diisopropyl 15 amide and potassium amide), aliphatic or aromatic lithium compounds (such as n-butyl lithium, t-butyl lithium and phenyl lithium), and the like. These materials are selected optionally depending on the reactivity of the aimed reaction.

20 This reaction is conducted usually at a temperature in the range of from  $-20^{\circ}\text{C}$  to  $100^{\circ}\text{C}$ , preferably from  $-10^{\circ}\text{C}$  to  $30^{\circ}\text{C}$  for 0.1 to 10 hours.

Process 5 Preparation of Compound (I-2) [Step E] and Deprotection of  $R^{10}$

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(wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>10</sup>, R<sup>n</sup>, X<sup>1</sup> and X<sup>2</sup> are as defined above, and R<sup>12</sup> is an appropriate leaving group in nucleophilic displacement in the present reaction, examples of which include a halogen such as chloro, bromo and iodo, and an aromatic or aliphatic sulfonyloxy group such as p-toluenesulfonyloxy, benzenesulfonyloxy and methanesulfonyloxy).

A compound of the formula (I) other than the one wherein R<sup>4</sup> and R<sup>7</sup> together form a bond, i.e. a compound of the formula (I-2), can be obtained by reacting a compound of the formula (V) with an indole derivative of the formula (VI). The compound of the formula (V) used herein is a well known compound or can be synthesized by a method disclosed in "Ukr. Khim. Zh." (vol. 16, p. 545, 1950), "J. Med. Chem." (vol. 34, p. 1538, 1991), "J. Prakt. Chem." (vol. 2, 79, p. 259 (1909), "J. Prakt. Chem." (vol. 2, 99, p. 56 (1919) or Japanese Unexamined Patent Publication No. 216882/1984. The compound of the formula (V) wherein R<sup>10</sup> is hydrogen, is used in this

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reaction preferably after displacing its acidic hydrogen with an appropriate substituent (such as Tr: trityl) by a known method.

This reaction is conducted usually in an appropriate 5 organic solvent in the presence of base. Examples of the solvent thus used include aprotic polar organic solvents (such as HMPA: hexamethylphosphoric triamide and DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidine), ethers (such as THF: tetrahydrofuran) and alkoxyalkanes, and the 10 solvent may be used respectively alone or in a mixture.

Examples of the base thus used include a strong base such as alkali metal amides (e.g. LDA: lithium diisopropyl amide, sodium amide and potassium amide) and aliphatic or aromatic lithium compounds (e.g. n-butyl lithium, t-butyl 15 lithium and phenyl lithium). These materials are selected optionally depending on the reactivity of the aimed reaction.

The reaction using a compound of the formula (V) wherein R<sup>4</sup> and R<sup>10</sup> are hydrogen, can be conducted in 20 accordance with a method disclosed in "J. Labelled Compounds and Radiopharmaceuticals" (vol. XXVIII, No. 8, p. 911, 1990). In such a case, a compound of the formula (V) is reacted with n-butyl lithium usually in an inert gas atmosphere such as nitrogen and in a mixed solvent 25 such as THF: HMPA=4:1 at a temperature of from -100°C to -10°C to form an anion, which is then reacted with an indole compound of the formula (VI) to obtain a compound

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of the formula (I-2). The reaction of the anion and the indole compound (VI) is conducted usually at a temperature of from -50°C to 100°C, preferably from -10°C to room temperature. The reaction time may be varied  
5 depending on the materials used, but is usually from 0.5 to 1 hour for the formation of an anion and from 0.5 to 5 hours for the reaction with an indole compound.

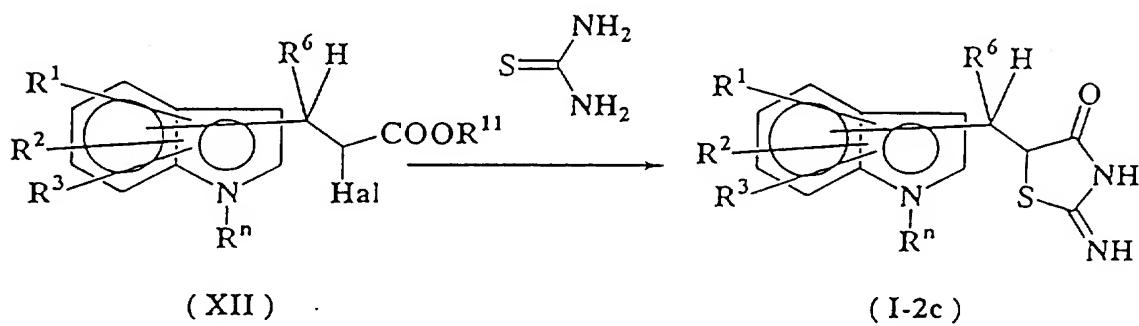
Also, this reaction can be conducted in accordance with a method disclosed in "J. Amer. Chem. Soc." (vol. 10 87, p. 4588, 1965) or "J. Med. Chem." (vol. 34, p. 1538, 1991). In such a case, a compound of the formula (V) is reacted with magnesium methylcarbonate in an inert gas atmosphere such as nitrogen and in an aprotic polar organic solvent such as dimethylformamide to form a  
15 chelate compound, and the chelate compound thus formed is further reacted with an indole compound of the formula (VI) to obtain a compound of the formula (I-2). This reaction is conducted usually at a temperature ranging from 20°C to 150°C, preferably from 70°C to 100°C. The  
20 reaction time varies depending on the materials used, but the formation of the chelate compound takes from 0.5 to 2 hours and the reaction with the indole compound takes from 0.5 to 5 hours.

In some cases, an amide group at the 3-position of  
25 thiazolidine ring of the compound of the formula (I-2) thus obtained may be deprotected by a well-known method. When R<sup>10</sup> is Tr (trityl), this method is conducted by

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using an organic acid such as trifluoroacetic acid and trichloroacetic acid or an inorganic acid such as hydrochloric acid and sulfuric acid. This reaction is conducted in the absence of a solvent or in the presence of a solvent such as ethers including tetrahydrofuran and dioxane and halogenated solvents including chloroform and dichloromethane, at a temperature ranging from 0°C to 100°C, preferably from 10°C to 50°C, for 0.1 to 5 hours.

## Process 6



15 (R<sup>4</sup>,R<sup>7</sup>,R<sup>10</sup>=H, X<sup>1</sup>=S, X<sup>2</sup>=NH)  
 (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>6</sup> are as defined above, and R<sup>11</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, and Hal is a halogen atom such as a chlorine atom, a bromine atom and an iodide atom).

20 A compound of the formula (I) wherein  $R^4$  and  $R^7$  are H and  $X^1$  is S and  $X^2$  is NH, i.e. a compound of the formula (I-2c) ( $R^4$ ,  $R^7$ =H,  $X^1$ =S,  $X^2$ =NH), can be obtained by reacting thiourea with a halocarboxylic acid ester of the formula (XII).

25 This reaction is conducted usually in an appropriate organic solvent in the presence of base or acid. Examples of the solvent used include alcohols,

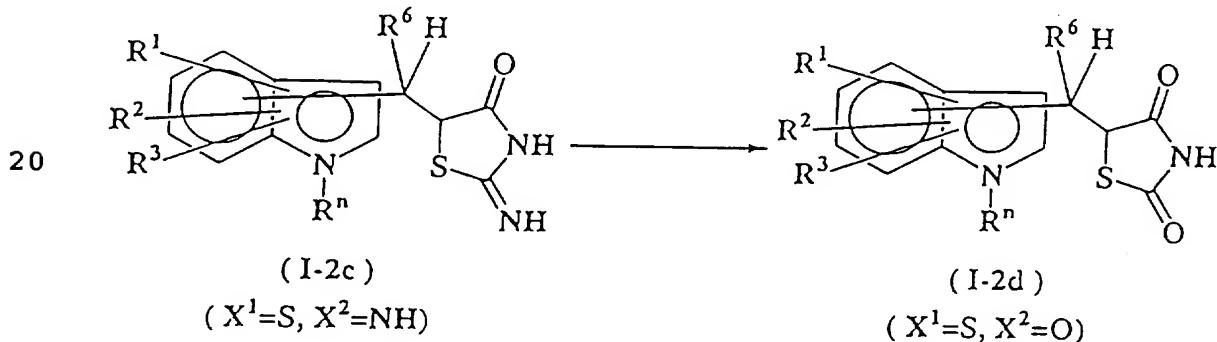
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cellosolves and aprotic polar organic solvents, preferably sulfolane.

This reaction is conducted at a temperature of from 0°C to a boiling point of a solvent used, preferably from 5 50°C to 150°C, for 0.5 to 10 hours.

As the reaction proceeds, a hydrogen halide is by produced, but the reaction can be accelerated by capturing the by-produced hydrogen halide with an appropriate base. Examples of the base used include 10 organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), inorganic alkali metal salts (such as sodium acetate and 15 potassium acetate) and the like.

#### Process 7



(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^6$  and  $R^n$  are as defined above).

25 A compound of the formula (I-2c) ( $X^1=S$ ,  $X^2=NH$ ), can be converted into a compound of the formula (I-2d) ( $X^1=S$ ,  $X^2=O$ ) by hydrolyzing an imino group at the 2-position of

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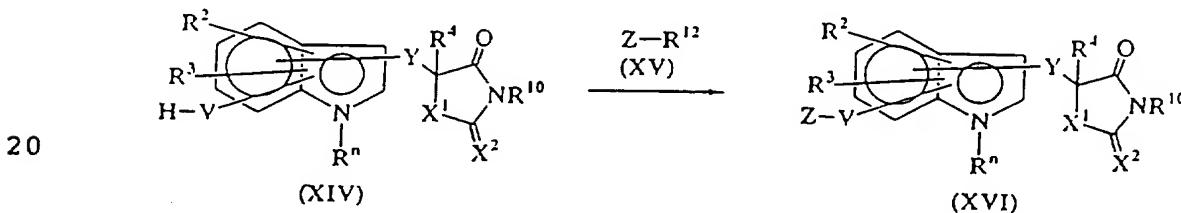
thiazolidine by a well known method.

This reaction is conducted usually in the presence of water and an acid in an appropriate organic solvent.

Examples of the solvent include usually alcohols, 5 cellosolves, aprotic polar organic solvents, ethers and alkoxy alkanes, preferably methanol, ethanol, methoxyethanol, sulfolane, dioxane and dimethoxyethane. Examples of the acid include inorganic acids (such as hydrochloric acid, sulfuric acid and hydrobromic acid), 10 and these materials are selected optionally depending on the reactivity of the aimed reaction.

This reaction is conducted usually at a temperature in the range of from 50°C to a boiling point of a solvent used in the reaction, preferably from 80°C to 150°C. The 15 reaction time is usually from 0.5 to 30 hours.

#### Process 8



(wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^{10}$ ,  $R^{12}$ ,  $X^1$ ,  $X^2$ ,  $Y$ ,  $V$  and  $Z$  are as defined above).

An indole compound ( $R^1=-V-Z$ ) of the formula (XVI) can 25 also be obtained by reacting a compound of the formula (XV) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIV) by a

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nucleophilic substitution reaction. The compound of the formula (XIV) is preferably protected by substituting hydrogen of  $R^{10}$  with an appropriate substituent (such as Tr: trityl).

5 This reaction is usually conducted in an appropriate organic solvent in the presence of base. Examples of the solvent used include aprotic polar organic solvents, ethers, aromatic hydrocarbons, hydrogenated hydrocarbons, alkoxyalkanes, acetonitrile, and the like.

10 Examples of the base thus used include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), Acid Captor H: 15 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one and Acid Captor 9M: 9-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one), metal alkoxides (such as sodium methoxide, sodium ethoxide, lithium isopropoxide and potassium t-butoxide), inorganic alkali metal salts (such 20 as sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydride, sodium acetate and potassium acetate), and alkali metal amides (such as sodium amide). These 25 materials are selected appropriately depending on the reactivity of the aimed reaction.

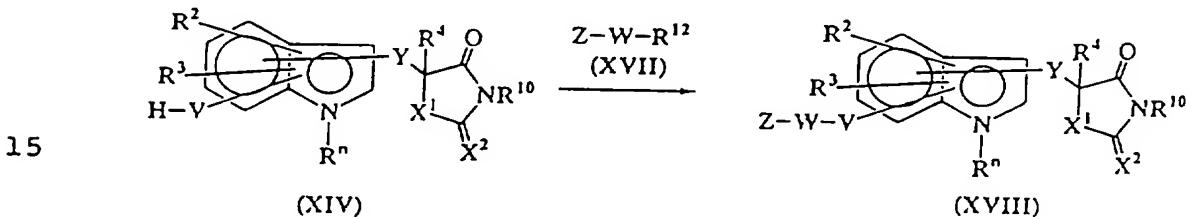
This reaction is conducted usually at a temperature

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ranging from -20°C to a boiling point of the solvent used, preferably from 20°C to 150°C, for from 0.5 to 30 hours.

Among compounds thus obtained, the one having a 5 protecting group on the thiazolidine ring as represented by the formula (XVI), can be led to a compound of the formula (I) either in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis" (1991) or deprotecting the 10 amide group at the 3-position of the thiazolidine ring by the method described in Process 5.

Process 9



(wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>10</sup>, R<sup>n</sup>, X<sup>1</sup>, X<sup>2</sup>, Y, V, W and Z are as defined above).

An indole compound (R<sup>1</sup>=-V-W-Z) of the formula 20 (XVIII), can also be obtained by reacting a compound of the formula (XVII) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIV) by nucleophilic substitution reaction. The compound of the formula (XIV) is preferably protected by 25 substituting hydrogen of R<sup>10</sup> with an appropriate substituent (such as Tr: trityl).

Among compounds of the formula (I), a compound

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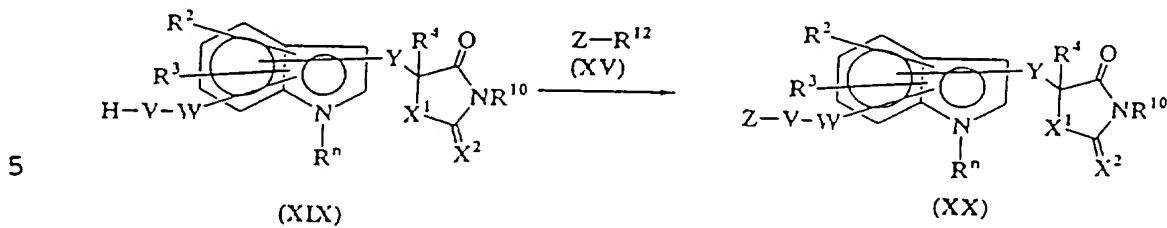
wherein  $R^1$  is  $-V-W-Z$  and  $W$  is  $COCH_2$ , can be obtained by using a compound of  $Z-COCH_2-Hal$  ( $W=COCH_2$ ,  $R^{12}=Hal$ ,  $Z$  and  $Hal$  are substituents explained above). Such a compound is well known and is commercially available, or can be 5 obtained by a well known method (for example, British Laid Open Patent Publication No. 1107677 discloses a compound wherein  $Z$  is pyrrole, Japanese Unexamined Patent Publication No. 85372/1986 discloses a compound wherein  $Z$  is oxazole or thiazole and U.S. Patent No. 4,167,626 10 discloses a compound wherein  $Z$  is triazole). Also, such a compound can be obtained by halogenating  $Z-COCH_3$  (for example, "Bull. Soc. Chim. Fr., p. 1760 (1973)" discloses a compound wherein  $Z$  is furan, "Tetrahedron, 29(2), p. 413 (1973)" discloses a compound wherein  $Z$  is thiophene, 15 "J. Heterocyclic Chem., 27(5), p. 1209 (1990)" discloses a compound wherein  $Z$  is pyrrole, "Bull. Soc. Chim. Fr., p. 540 (1988)", "Bull. Soc. Chim. Fr., p. 318 (1987)", "J. Heterocyclic Chem., 23(1), P. 275 (1986)", "Arch. Pharm., 316(7), p. 608 (1983)" and "Synlett., (7), p. 483 20 (1991)" disclose a compound wherein  $Z$  is pyrazole, "J. Heterocyclic Chem., 17(8), p. 1723 (1980)" discloses a compound wherein  $Z$  is imidazole, and "J. Chem. Soc. C(20), p. 2005 (1976)" and "Heterocycles, 26(3), p. 745 25 (1987)" disclose a compound wherein  $Z$  is triazole) as a starting material by means of an appropriate well known halogenation method (e.g. a method disclosed in Japanese Unexamined Patent Publication No. 85372/1986). Also,

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such a compound can be obtained by subjecting  $Z-CO_2R'$  (R'=lower alkyl or substituted or unsubstituted benzyl) (for example, "Z. Chem., 9(1), p. 22 (1969)" and "Synth. Commun., 20(16), p. 2537 (1990)" disclose a compound 5 wherein Z is thiophene, "J. Org. Chem., 55(15), p. 4735 (1990)" and "Chem. Pharm. Bull., 17(3), p. 582 (1969)" disclose a compound wherein Z is pyrrole, European Laid Open Patent Publication No. 506194 discloses a compound wherein Z is imidazole, and "Chem. Ber., 117(3), p. 1194 10 (1984)" discloses a compound wherein Z is pyrazole or triazole) as a starting material to an appropriate well known reduction-oxidation reaction (for example, reduction by diisobutyl aluminum hydride and then 15 oxidation by manganese dioxide) to obtain Z-CHO, and further by converting the product thus obtained to Z-COCH<sub>2</sub>-hal by an appropriate method (e.g. a method disclosed in "Tetrahedron Letters, p. 4661 (1972)").

This reaction can be conducted in the same manner as in the Process 8.

20 Among compounds thus obtained, the one having a protecting group on the thiazolidine ring as represented by the formula (XVIII), can be led to a compound of the formula (I) either in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts in "Protective 25 Groups in Organic Synthesis" (1991) or deprotecting the amide group at the 3-position of the thiazolidine ring by the method described in Process 5.

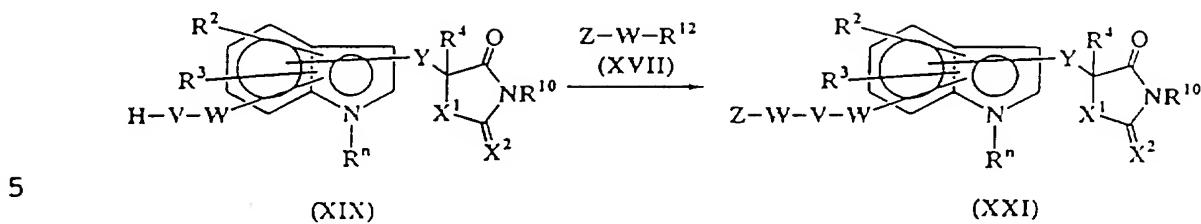
Process 10

(wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^{10}$ ,  $R^{12}$ ,  $R^n$ ,  $X^1$ ,  $X^2$ ,  $Y$ ,  $V$ ,  $W$  and  $Z$  are as defined above).

10 An indole compound ( $R^1=-W-V-Z$ ) of the formula (XX) can also be obtained by reacting a compound of the formula (XV) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIX) by nucleophilic substitution. The compound of the formula 15 (XIX) is preferably protected by substituting hydrogen of  $R^{10}$  with an appropriate substituent (such as Tr: trityl).

This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, the compound 20 having a protective group introduced into a thiazolidine ring part of the formula (XX) can be converted into a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Greene, 25 P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the Process 5.

Process 11

(wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^{10}$ ,  $R^{12}$ ,  $R^n$ ,  $X^1$ ,  $X^2$ ,  $Y$ ,  $V$ ,  $W$  and  $Z$  are as defined above).

An indole compound ( $R^1=-W-V-W-Z$ ) of the formula (XXI) 10 can also be obtained by reacting a compound of the formula (XVII) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIX). The compound of the formula (XIX) is preferably protected by substituting hydrogen of  $R^{10}$  with an appropriate 15 substituent (such as Tr: trityl).

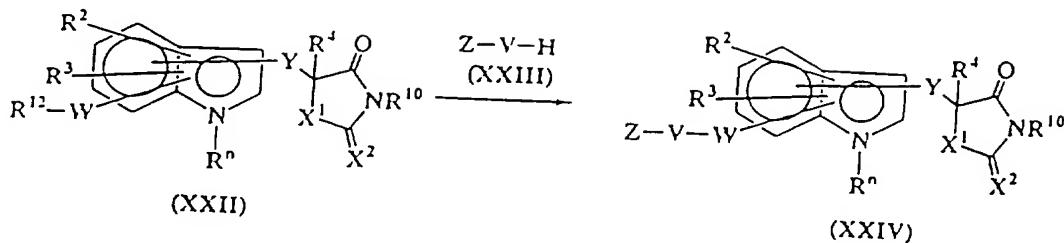
This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, the compound having a protective group introduced into a thiazolidine 20 ring part of the formula (XXI) can be converted to a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Green, P.G.M. Wuts "Protective Groups in Organic Synthesis" 25 (1991) or the method disclosed in the above Process 5.

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Process 12

5



(wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^{10}$ ,  $R^{12}$ ,  $R^n$ ,  $X^1$ ,  $X^2$ ,  $Y$ ,  $V$ ,  $W$  and  $Z$  are as defined above).

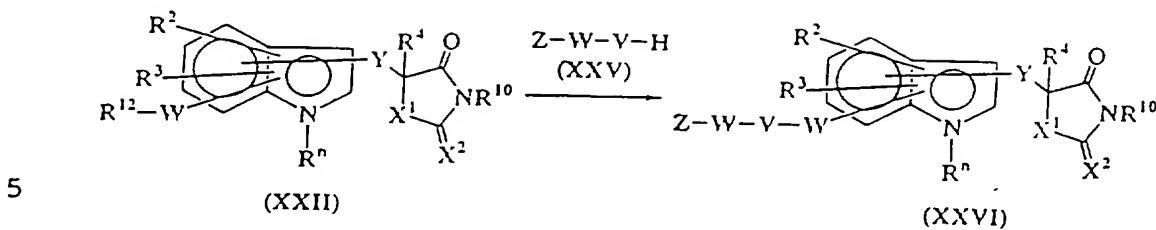
An indole compound ( $R^1=-W-V-Z$ ) of the formula (XXIV) 10 can also be obtained by reacting an indole compound of the formula (XXII) with a hydroxyl group, a thiol group or an amino group of a compound of the formula (XXIII) by nucleophilic substitution. The compound of the formula (XXII) is preferably protected by substituting hydrogen 15 of  $R^{10}$  with an appropriate substituent (such as Tr: trityl).

This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, a compound having 20 a protective group introduced into a thiazolidine ring part of the formula (XXIV) can be converted to a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts 25 "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the above Process 5.

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### Process 13



(wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^{10}$ ,  $R^{12}$ ,  $R^n$ ,  $x^1$ ,  $x^2$ ,  $y$ ,  $v$ ,  $w$  and  $z$  are as defined above).

An indole compound ( $R^1 = -W-V-W-Z$ ) of the formula (XXVI) can also be obtained by reacting an indole compound of the formula (XXII) with a hydroxyl group, a thiol or an amino group of a compound of the formula (XXV). The compound of the formula (XXII) is preferably protected by substituting hydrogen of  $R^{10}$  with an appropriate substituent (such as Tr: trityl).

This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, a compound having a protective group introduced into a thiazolidine ring part of the formula (XXVI) can be converted to a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the above Process 5.

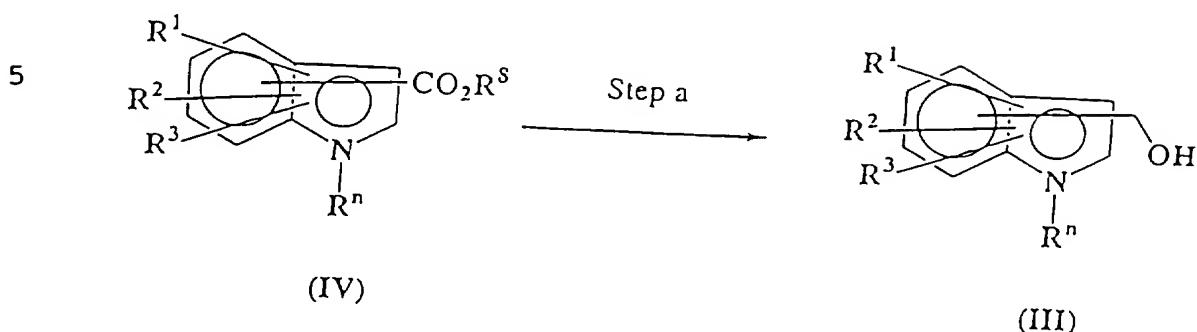
Now, the processes for producing intermediates useful for the preparation of the compounds of the present

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invention will be described hereinafter.

### Method for preparing intermediate (III)

### Synthesis Route 1 (Step a)



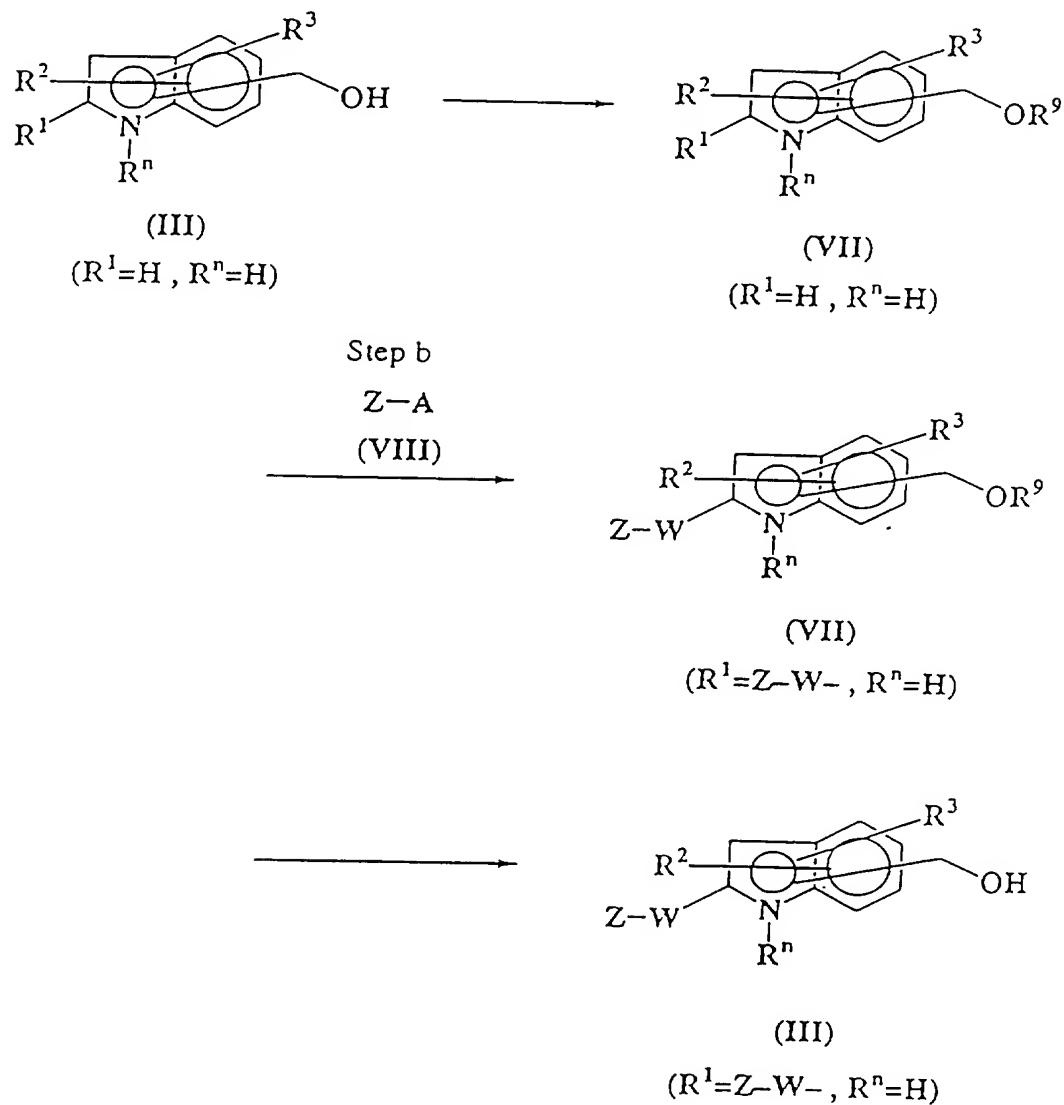
10 (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>n</sup> are as defined above, and R<sup>8</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a phenyl group or a benzyl group).

A hydroxymethylindole (intermediate (III)) is available by using a commercial available reagent or by reducing a carboxyl indole of the formula (IV) or an alkoxy carbonylindole.

The step of synthesizing the compound of the formula (III) can be conducted by using a well known appropriate reducing agent (e.g. metal hydride complex compounds such 20 as LAH: lithium aluminum hydride, SAH: sodium aluminum hydride, sodium triethoxyaluminum hydride, Red-Al: sodium bis(2-methoxyethoxy) aluminum hydride, SBH: sodium borohydride and LBH: lithium borohydride, and metal hydride compounds such as DIBAH: diisobutyl aluminum 25 hydride, and catalytic hydrogenation using CuBaCrO as a catalyst).

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Synthesis Route 2 Introduction of substituent  $R^1$  into the 2-position of indole



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(wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>n</sup>, W and Z are as defined above, and R<sup>9</sup> is a protecting group (such as t-butyldimethylsilyl group) of a primary hydroxymethyl group).

5 Among hydroxymethyl indole compounds of the formula (III), a compound having a hydrogen atom at the 2-position of an indole ring can get a carbon functional group: R<sup>1</sup> (Z-W-, Z-V-W-, Z-W-V- and Z-V-) introduced at the 2-position by means of the following method.

10 (Protection of hydroxymethyl group)

In this synthesis route, a compound (VII) can be obtained by protecting a primary hydroxymethyl group of hydroxymethyl indole of the formula (III) by means of a well known method. For example, protection of these 15 alcohols can be conducted in accordance with the method disclosed by T.W. Greene, P.G M. Wuts in "Protective Groups in Organic Synthesis" (1991). A protective group: R<sup>9</sup> is preferably stable under basic conditions in the following step, examples of which include a substituted 20 silyl group (such as trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl and 25 t-butyloxymethoxyphenylsilyl), a substituted acyl group (such as chloroacetyl, dichloroacetyl, trichloroacetyl, fluoroacetyl, difluoroacetyl, trifluoroacetyl and

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pivaloyl), benzoyl, a substituted alkoxy carbonyl group (such as methoxycarbonyl, ethoxycarbonyl, t-butylloxycarbonyl and i-butyloxycarbonyl), and the like, particularly preferably triisopropylsilyl, t-  
5 butyldimethylsilyl, t-butyldiphenylsilyl and the like. When the protective group is t-butyldimethylsilyl, this reaction is conducted by using t-butyldimethylsilyl chloride in dimethylformamide in the presence of imidazole at room temperature in accordance with J. Amer.  
10 Chem. Soc., vol. 94, P 6190 (1972).

(Step b)

In Step b, at the 2-position of the indole ring of the compound (VII) thus obtained, a carbon functional group: Z-W-, Z-V-W- or Z-V- can be introduced in  
15 accordance with the method disclosed by A. R. Kartitzky, "Tetrahedron Letters" vol. 26(48), P5935 (1985).

A compound of the formula (VIII) means an electrophilic reagent which can be reacted with an indole ring metalated in step b. Examples of a substrate usable  
20 in such a reaction are illustrated below. For example, in the case of synthesizing a compound of the formula (VII) wherein W is  $-\text{CH}_2-$  ( $\text{R}^{\text{d}}=\text{H}$ ,  $\text{R}^{\text{e}}=\text{H}$ ,  $\text{m}=1$ ), a compound of the formula Z-A (A is  $-\text{CH}_2-\text{B}$  (B is a leaving group in this reaction, such as a chlorine atom, a bromine atom,  
25 an iodine atom, methanesulfonyl, benzenesulfonyl and p-toluenesulfonyl)) can be employed. When synthesizing a compound of the formula (VII) wherein W is  $-\text{C}(=\text{O})-$  ( $\text{R}^{\text{d}}$

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and  $R^e$  together form an oxo group and  $m=1$ ), a compound of the formula  $Z-A$  ( $A$  is  $-C(=O)-B$  ( $B$  is a leaving group in this reaction, such as  $OH$ ,  $OLi$ ,  $ONa$ ,  $OK$ , a chlorine atom, a bromine atom, an iodine atom and methoxymethylamino, 5 preferably  $OK$ , a chlorine atom, a bromine atom and methoxymethylamino)) can be employed. In the case of synthesizing a compound of the formula (VII) wherein  $W$  is  $-C(OH)H-$  ( $R^d=H$ ,  $R^e=OH$ ,  $m=1$ ), a compound of the formula  $Z-A$  ( $A$  is  $-CHO$ ) can be employed. In the case of 10 synthesizing a compound of the formula (VII) wherein  $W$  is  $-C(OH)R^d-$  ( $R^d=Me$  or  $Ph$ ,  $R^e=OH$ ,  $m=1$ ), a compound of the formula  $Z-A$  ( $A$  is  $-C=O)-R^d$  ( $R^d=Me$  or  $Ph$ )) can be employed. In the case of synthesizing a compound of the formula (VII) wherein  $V$  is  $-S-$ , a compound of the formula 15  $Z-A$  ( $A$  is  $-S-S-Z$ ) can be employed.

When synthesizing a compound of the formula (VII) wherein  $V$  is  $-SO_2-$ , a compound of the formula  $Z-W-A$  or  $Z-A$  ( $A$  is  $SO_2-B$  ( $B$  is an eliminated group in this reaction, such as a halogen atom, preferably a chlorine atom)) can 20 be employed. When synthesizing a compound of the formula (VII) wherein  $W-V$  is  $CO-NH$ , a compound of the formula  $Z-A$  ( $A$  is  $-N=C=O$ ) can be employed.

A compound of the formula (VIII) may be a commercially available reagent or can be synthesized by a 25 well known method.

In this case, lithium tetrahydrofuran, sodium hydroxide, potassium hydroxide, lithium, sodium,

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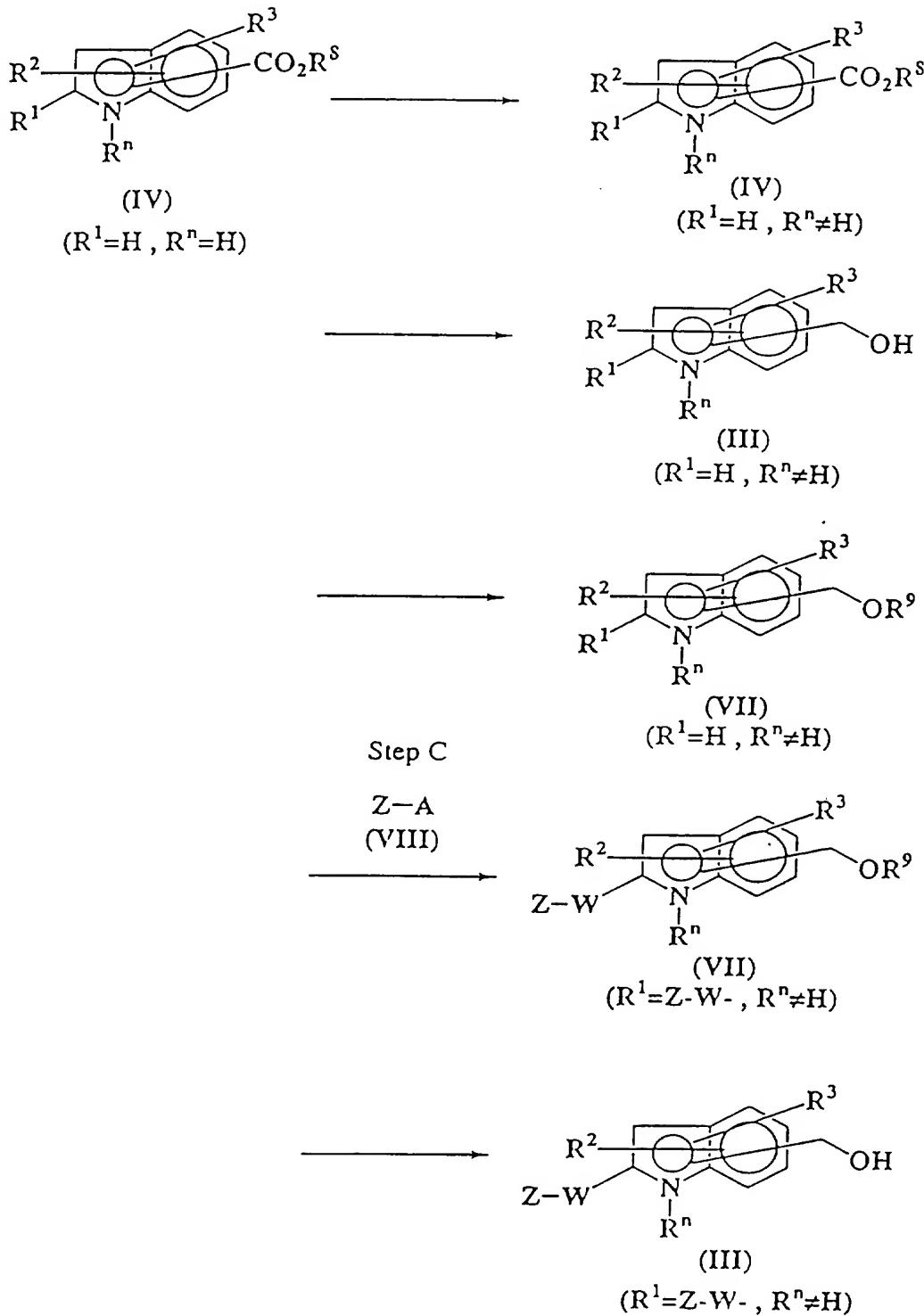
potassium, zinc, magnesium or copper, preferably s-butyl lithium or t-butyl lithium is used in an inert gas atmosphere such as nitrogen or argon. For example, in the case of using t-butyl lithium, the reaction is 5 conducted at a temperature of from -100°C to 100°C, preferably at -78°C, for 1 to 2 hours, and the reaction with a compound of the formula (VIII) is then conducted at -78°C. Thereafter, the reaction temperature is returned to room temperature, and a saturated ammonium 10 chloride aqueous solution is added thereto, and the reaction mixture is heated at 80°C-120°C to obtain a compound of the formula (VII) or to isolate a carboxylic acid compound (VII)  $R^n=COOH$  by recrystallization, which is then heated at 80°C-200°C to conduct decarboxylation.

15 (Deprotection of hydroxymethyl group)

Deprotection of a primary hydroxymethyl group is conducted by means of a well known method. For example, deprotection of these alcohols is conducted in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts 20 "Protective Groups in Organic Synthesis" (1991) to obtain a compound (III) wherein  $R^1$  is introduced at the 2-position. When  $R^9$  is t-butyldimethylsilyl, this reaction is conducted by using tetra-n-butylammonium fluoride in THF: Tetrahydrofuran at 0°C-30°C in accordance with the 25 method disclosed in J. Amer. Chem. Soc., vol. 94, P6190(1972).

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Synthesis Route 3 Introduction of substituent  $R^1$  at the 2-position of indole



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(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^8$ ,  $R^9$ ,  $R^n$ ,  $W$  and  $Z$  are as defined above).

Among alkoxy carbonyl indoles of the formula (IV), a compound having an indole ring having hydrogen at the 1-position and the 2-position can be converted to the corresponding hydroxymethyl indole (compound (III)) by introducing a carbon functional group:  $R^1$  ( $Z-W-$ ) by means of the following method.

The alkoxy carbonyl indole of the formula (IV) used 10 may be a commercially available reagent or may be obtained by esterifying indole carboxylic acid as a starting material by a well known method.

(Displacement of  $R^n$  substituent)

In this synthesis route, firstly a substituent:  $R^n$  15 ( $\neq H$ ) is introduced at the 1-position of an indole ring of alkoxy carbonyl indole (IV). Examples of  $R^n$  include a  $C_1-C_7$  alkyl group, a  $C_1-C_4$  alkoxy methyl group, a  $C_1-C_4$  alkylaminomethyl group, a carboxyl group, a  $C_1-C_4$  alkoxy carbonyl group, a  $C_1-C_4$  alkylaminocarbonyl group, a 20  $C_1-C_7$  alkoxy group, a  $C_1-C_7$  alkoxy alkyl methoxy group, an alkylsulfonyl group and an aryl sulfonyl group, preferably methyl, methoxymethyl, dimethylaminomethyl, carboxyl, t-butyloxycarbonyl, methylcarbamoyl, methoxy, methoxymethoxy, mesyl, benzene sulfonyl, p-toluenesulfonyl, p-methoxybenzenesulfonyl, p-fluorobenzenesulfonyl and p-chlorobenzenesulfonyl, more preferably benzene sulfonyl. When  $R^n$  is  $PhSO_2^-$ , this

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reaction is conducted by using benzenesulfonyl chloride, sodium hydride and n-butyl lithium in dimethylformamide at 0°C- 100°C in accordance with the method disclosed by R.J. Sundberg, "J. Org. Chem." vol. 38(19), P3324 (1973).

5 (Reduction of alkoxy carbonyl group)

The alkoxy carbonyl group of the compound (IV) thus obtained is reduced by using an appropriate reducing agent such as DIBAL: diisobutylaluminium hydride and LAH: lithium aluminum hydride by means of a well known method 10 to obtain the corresponding hydroxymethyl indole (compound (III)). This reaction is conducted, for example, in THF at 0°C-50°C.

(Protection of hydroxymethyl group)

The primary hydroxymethyl group of the hydroxymethyl 15 indole (compound (III)) is protected by means of a well known method to obtain a compound (VII). A protective group: R<sup>9</sup> should be preferably stable under basic conditions in the following step, and the same protective group as used in Synthesis Route 1 can be used. For 20 example, when a t-butyldimethylsilyl group is used, a protective group can be introduced in the same manner as in Synthesis Route 1.

(Step c)

In the compound (VII) thus obtained, a carbon 25 functional group R<sup>1</sup> can be introduced at the 2-position of the indole ring in accordance with the method disclosed by R.J. Sundberg, "J. Org. Chem.", vol. 38

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(19), P3324 (1973).

In this reaction, a compound of the formula (VII) is reacted with a base to anionize the 2-position under an inert gas atmosphere such as nitrogen or argon in an aprotic organic solvent such as tetrahydrofuran, ether, isopropyl ether, n-pentane, i-pentane, cyclopentene, n-hexane, cyclohexane, HMPA: hexamethylphosphoric triamide, HMPT: hexamethylphosphorous triamide, N,N,N',N'-tetramethylethylenediamine, dioxane, dimethylsulfoxide or 10 dimethylformamide. Examples of the base used include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl lithium, methyl lithium, LDA: lithium diisopropyl amide, potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, 15 lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium or copper, preferably n-butyl lithium, s-butyl lithium, t-butyl lithium or LDA. For example, when t-butyl lithium is used, the reaction is conducted at a temperature of from 20 -100°C to 100°C, preferably from -78°C to 0°C, for 10 to 120 minutes, and then the reaction with a compound of the formula (VIII) is conducted to introduce a carbon functional group at the 2-position of the indole ring. A compound of the formula (VIII) may be a commercially 25 available reagent or may be synthesized in the same manner as above.

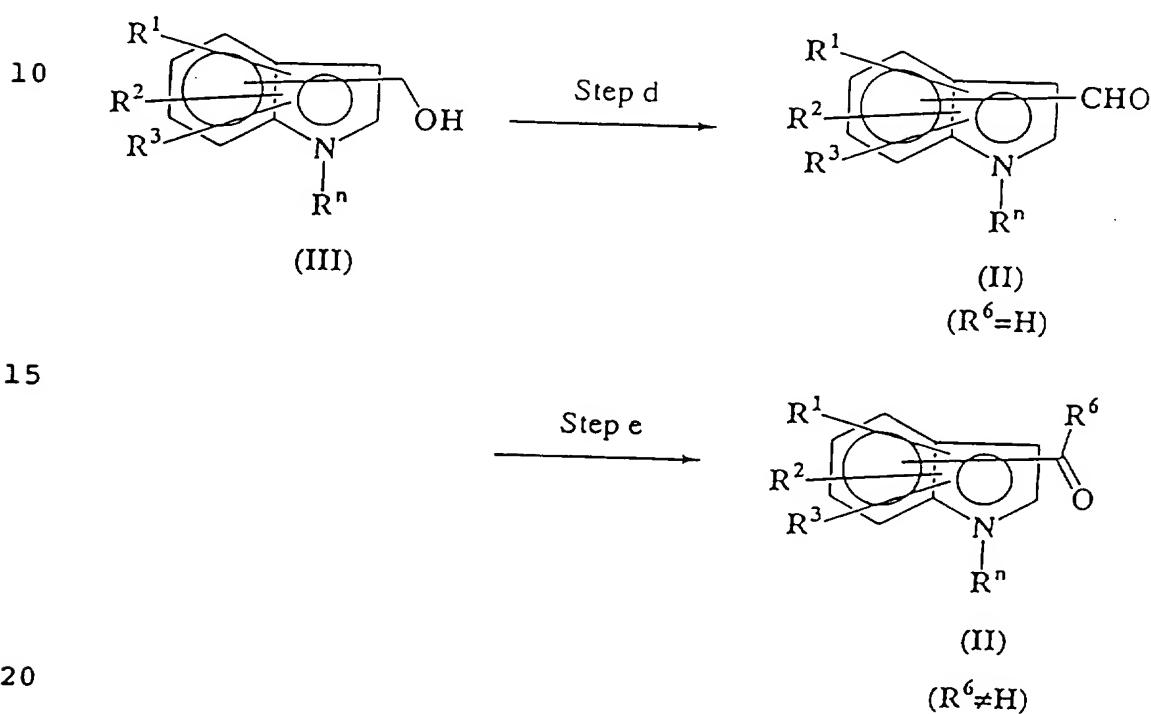
(Deprotection of hydroxymethyl group)

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The deprotection of a primary hydroxymethyl group is conducted by means of a well known method to obtain a compound (III) having  $R^1$  introduced at the 2-position. When  $R^9$  is t-butyldimethylsilyl, this reaction is conducted under the same conditions as in Synthesis Route 1.

### Method for preparing intermediate (II)

### Synthesis Route 1



(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^6$  and  $R^n$  are as defined above).

A carbonyl indole of the formula (II) is a well known compound or can be obtained by oxidizing a hydroxymethyl indole of the formula (III). This step is conducted by using an appropriate oxidizing agent (such as manganese dioxide, PCC: pyridiniumchlorochromate, PDC:

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pyridiniumdichromate, DDQ: dichlorodicyanobenzoquinone, chloranil, Swern oxidizing agent: oxalyl chloride-dimethylsulfoxide-tertiary amine or sulfur trioxide-pyridine complex).

5 An example of using pyridine chromic acid complex as an oxidizing agent is disclosed in Japanese Examined Patent Publication No. 34986/1974.

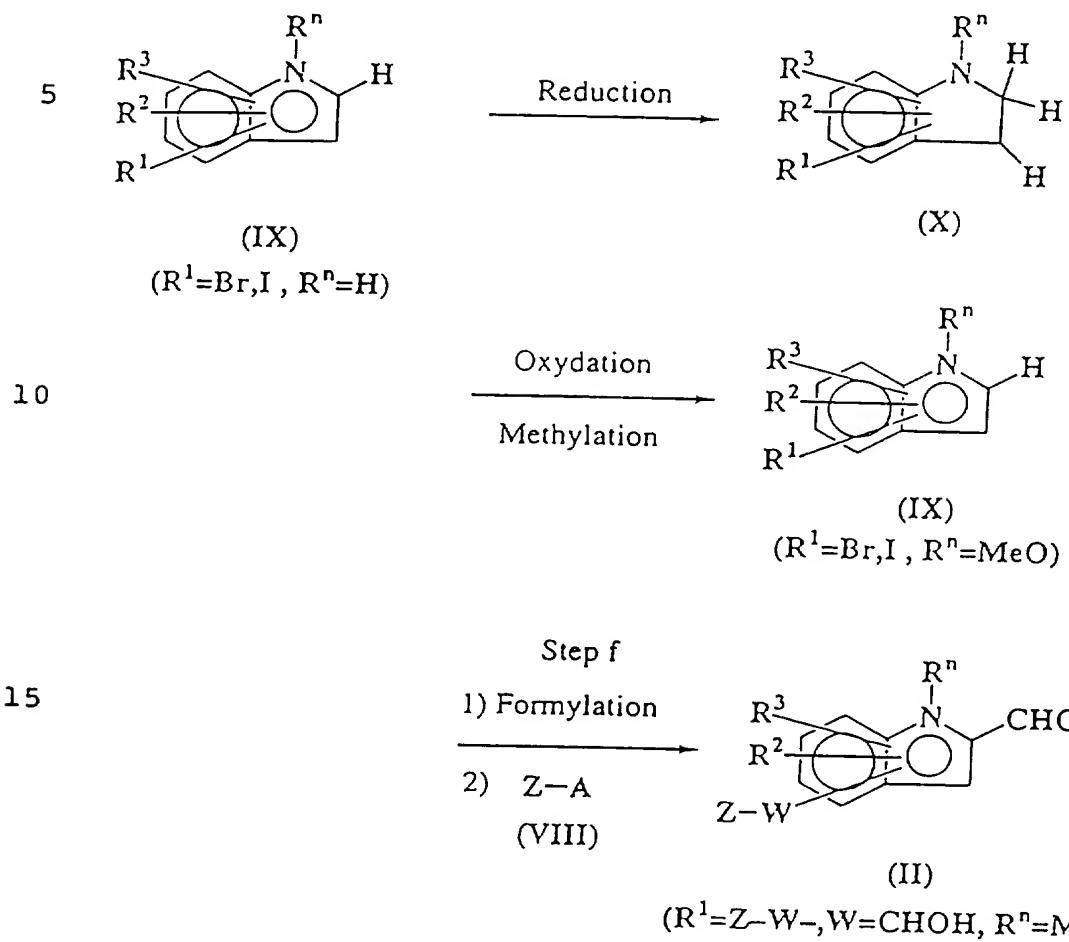
A formylindole of the formula (II) ( $R^6=H$ ) obtained by the above method can be converted to a carbonylindole of 10 the formula (II) ( $R^6\neq H$ ) by alkylating the formyl group with an appropriate alkylating agent.

This step can be conducted by the method using diazomethane as disclosed in "Tetrahedron Letters" P955 (1963) and "Chem. Ber." vol. 40, P479 (1907), the method 15 using alkyl halide as disclosed in "Synth. Commun." vol. 14(8), P743 (1984) or the method using alkyl lithium as disclosed in "J. Org. Chem." vol. 30, P226 (1965).

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Synthesis Route 2

Introduction of substituent  $R^1$  and formylation at the 2-position of indole



20 (wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^n$ ,  $W$  and  $Z$  are as defined above).

Among formylindoles of the formula (II) ( $R^6=H$ ), a compound having a formyl group at the 2-position of an indole ring and having a carbon functional group  $R^1$  at the 4-, 5-, 6- or 7-position can be synthesized by the 25 following method.

A carbon functional group:  $R^1$  can be introduced in the indole nucleus by protecting a nitrogen atom at the

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1-position of haloindole of the formula (IX) with a lower alkoxy group, particularly a methoxy group, conducting formylation at the 2-position, conducting metalation of the haloindole in the presence of a strong base and then 5 reacting with an aldehyde compound of the formula (XI).  
(Reduction of indole ring)

A haloindole (IX) used as a starting material has a hydrogen atom at the 1-position and a halogen atom at the 4-, 5-, 6- or 7-position. The halogen atom is preferably 10 bromine or iodine, more preferably bromine, and the haloindole (IX) used is a commercially available reagent or can be synthesized by a well known method. The haloindole (IX) can be converted into the corresponding indoline (compound (X)) by reducing at the 2- and 3- 15 positions of the indole ring, for example, by the method disclosed in "J. Amer. Chem. Soc. " vol. 96, P7812 (1974).

(Synthesis of methoxyindole by oxidation and methylation of indoline)

20 The indoline (compound (X)) can be converted into the corresponding 1-methoxyhaloindole (compound (IX)) by conducting oxidation and methylation at the 2-, 3- and 1-positions in accordance with the method disclosed in Japanese Unexamined Patent Publication No. 31257/1991 (M. 25 Somei). This reaction is conducted by oxidizing with a 30% hydrogen peroxide aqueous solution in a methanol/water mixture solvent in the presence of

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disodium tungstate dihydrate as a catalyst at 0°C and then methylating with diazomethane or dimethylsulfuric acid: potassium carbonate at room temperature.

(Step f)

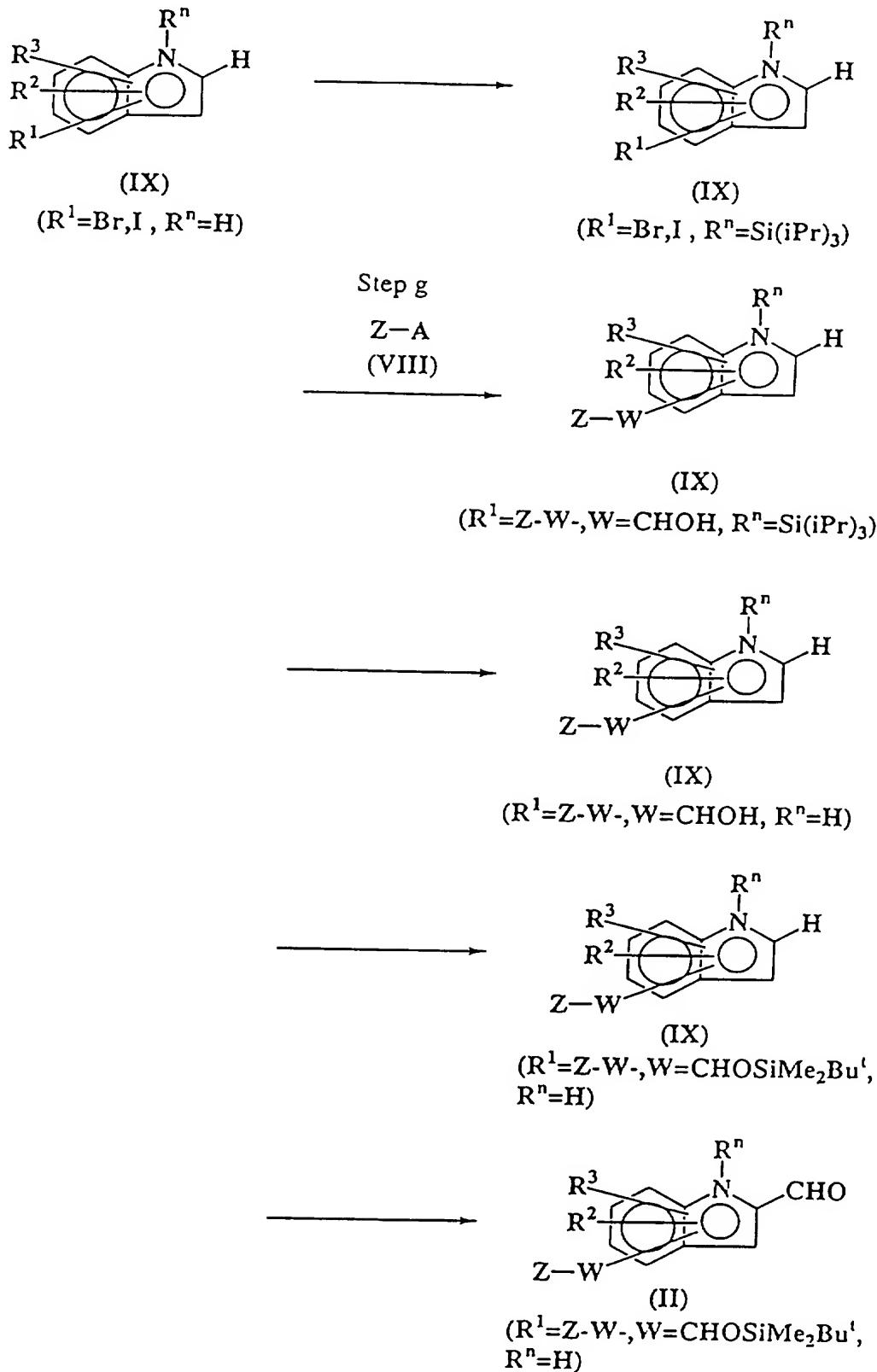
5 1-methoxyhaloindole (compound (IX)) can be converted to the aimed formylindole (compound (II)) by conducting formylation at the 2-position and then reacting with compound (VIII) in accordance with the method disclosed in "Heterocycles" by M. Somei, vol. 132, P221 (1991).

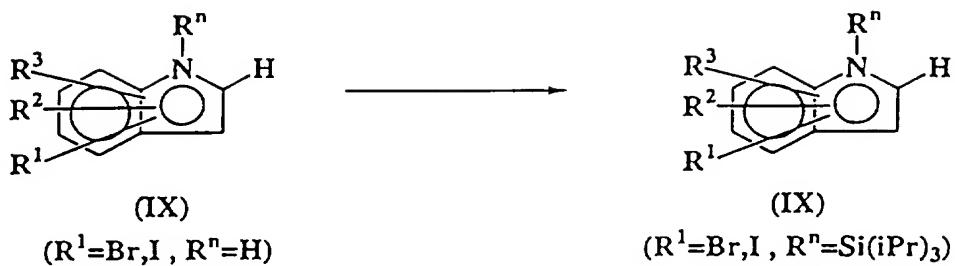
10 The 2-position of 1-methoxyhaloindole is anionized by reacting with a base under an inert gas atmosphere such as nitrogen or argon in an aprotic organic solvent such as tetrahydrofuran, ether, isopropyl ether, n-pentane, i-pentane, cyclopentane, n-hexane, cyclohexane, HMPA:

15 hexamethylphosphoric triamide, HMPT:  
hexamethylphosphorous triamide, N,N,N',N'-  
tetramethylethylene diamine, dioxane, dimethylsulfoxide  
or dimethylformamide. Examples of such a base include n-  
butyl lithium, s-butyl lithium, t-butyl lithium, phenyl  
20 lithium, methyl lithium, LDA: lithium diisopropyl amide,  
potassium bis(trimethylsilyl)amide, calcium hydride,  
sodium hydride, potassium hydride, potassium carbonate,  
lithium hydroxide, sodium hydroxide, potassium hydroxide,  
lithium, sodium, potassium, zinc, magnesium and copper,  
25 preferably phenyl lithium, n-butyl lithium and LDA. For  
example, when phenyl lithium is used, the reaction is  
conducted for 10-120 minutes by lithium-modifying the 2-

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position in tetrahydrofuran at a temperature of from - 100°C to 100°C, preferably from -78°C to 0°C, and reaction with N,N'-dimethylformamide, N,N'-methoxymethylformamide is then conducted for 5 to 120 5 minutes. Thereafter, the 5-position is anionized by further reacting with a base at a temperature of from - 100°C to 100°C, preferably from -78°C to 0°C. Examples of the base used include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl lithium, methyl lithium, 10 LDA: lithium diisopropylamide, potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium and copper, 15 preferably s-butyl lithium and t-butyl lithium. For example, when t-butyl lithium is used, after reacting for 10 to 120 minutes, reaction with the compound of the formula (VIII) is conducted to obtain the aimed formyl indole (compound (II)).

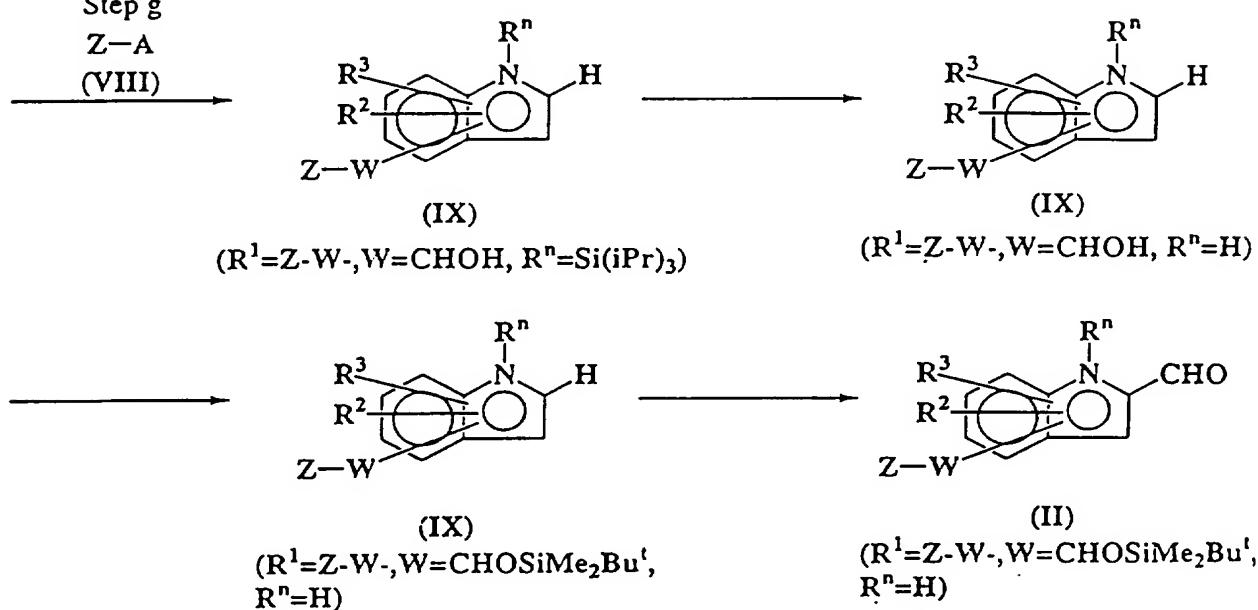
Synthesis Route 3



### Step 8

Z-A

(VIII)



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(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^n$ ,  $W$  and  $Z$  are as defined above).

Among formylindoles of the formula (II) ( $R^6=H$ ), an indole having a formyl group at the 2-position of the indole ring and having a carbon functional group:  $R^1$  at 5 the 4-, 5-, 6- or 7-position can be synthesized by the following method.

After protecting a nitrogen atom at the 1-position of a haloindole of the formula (IX) with a substituted silyl group, the haloindole is subjected to metalation in the 10 presence of a strong base and was reacted with an aldehyde compound of the formula (VIII) to introduce a carbon functional group into the indole ring. Thereafter, the silyl group at the 1-position is deprotected and the 2-position is formylated to obtain a 15 formylindole (intermediate (II)).

The haloindole (IX) ( $R^1=Br$ ,  $I$ ,  $R^n=H$ ) used as a starting material has a hydrogen atom at the 1-position and a halogen atom at the 4-, 5-, 6- or 7-position. The halogen atom is preferably bromine or iodine, more 20 preferably bromine and the haloindole used may be a commercially available reagent or may be prepared by a well known method.

(Introduction of substituent  $R^n$ )

An appropriate substituent is introduced into the 25 haloindole (IX) by a well known method. Examples of the substituent include a substituted silyl group, a  $C_1-C_7$  acyl group, a  $C_1-C_4$  alkoxy carbonyl group and a  $C_1-C_4$

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alkylaminocarbonyl group, preferably pivaloyl, t-butyl oxycarbonyl, t-butyl carbamoyl, triisopropylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl, more preferably triisopropylsilyl, t-butyldimethylsilyl and t-  
5 butyldiphenylsilyl.

(Step g)

The 5-position of the compound of the formula (IX) ( $R^1=Br$ , I,  $R^n=H$ ) is anionized by reacting with a base under an inert gas atmosphere such as nitrogen or argon  
10 in an aprotic organic solvent such as tetrahydrofuran, ether, isopropyl ether, n-pentane, i-pentane, cyclopentane, n-hexane, cyclohexane, HMPA: hexamethylphosphoric triamide, HMPT: hexamethylphosphorous triamide,  $N,N,N',N'$ -  
15 tetramethylene diamine, dioxane, dimethylsulfoxide or dimethylformamide, preferably tetrahydrofuran or ether. Examples of the bases used include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl lithium, methyl lithium, LDA: lithium diisopropyl amide,  
20 potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium and copper, preferably n-butyl lithium, s-butyl lithium, t-butyl lithium and methyl lithium. For example, when t-butyl lithium is used, the reaction is conducted in ether at a  
25 temperature of from  $-100^{\circ}C$  to  $100^{\circ}C$ , preferably  $-78^{\circ}C$  to

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0°C, for 10 to 120 minutes, and the reaction product is further reacted with a compound of the formula (VIII) to obtain a compound (IX) ( $R^1=Z-W-$ ,  $W=CHOH$ ,  $R^n=Si(iPr)_3$ ). (Removal of  $R^n$  substituent)

5 A compound of the formula (IX) ( $R^1=Z-W-$ ,  $W=CHOH$ ,  $R^n=Si(iPr)_3$ ) can be converted to a compound of the formula (IX) ( $R^1=Z-W-$ ,  $W=CHOH$ ,  $R^n=H$ ) by reacting with tetra-*n*-butylammonium fluoride in tetrahydrofuran or ether at room temperature.

10 (Protection of hydroxy group)

A compound of the formula (IX) ( $R^1=Z-W-$ ,  $W=CHOH$ ,  $R^n=H$ ) can be converted to a compound of the formula (IX) ( $R^1=Z-W-$ ,  $W=C(H)OSiMe_2t-Bu$ ,  $R^n=H$ ) by reacting with tertiary butyldimethylsilyl chloride in the presence of

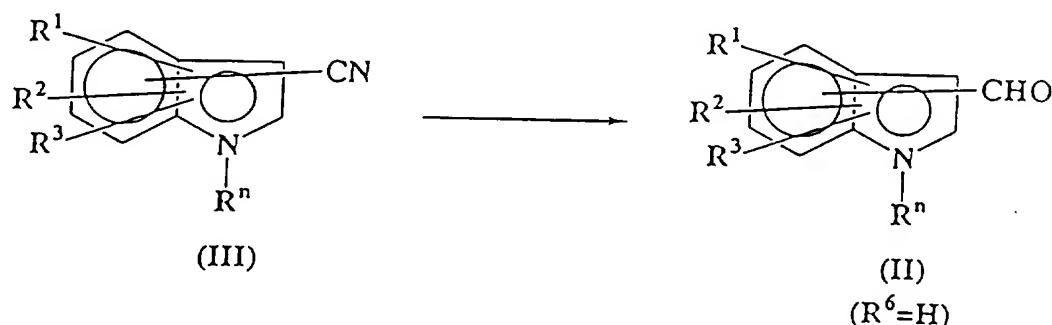
15 imidazole in dimethylformamide.

(Formylation at the 2-position of indole ring)

A compound of the formula (IX) ( $R^1=Z-W-$ ,  $W=C(H)OSiMe_2t-Bu$ ,  $R^n=H$ ) can be converted into a formylated product (II) by the method disclosed in "J.

20 Am. Chem. Soc." of A. R. Katritzky, vol. 108, p 6808 (1986).

#### Synthesis Route 4



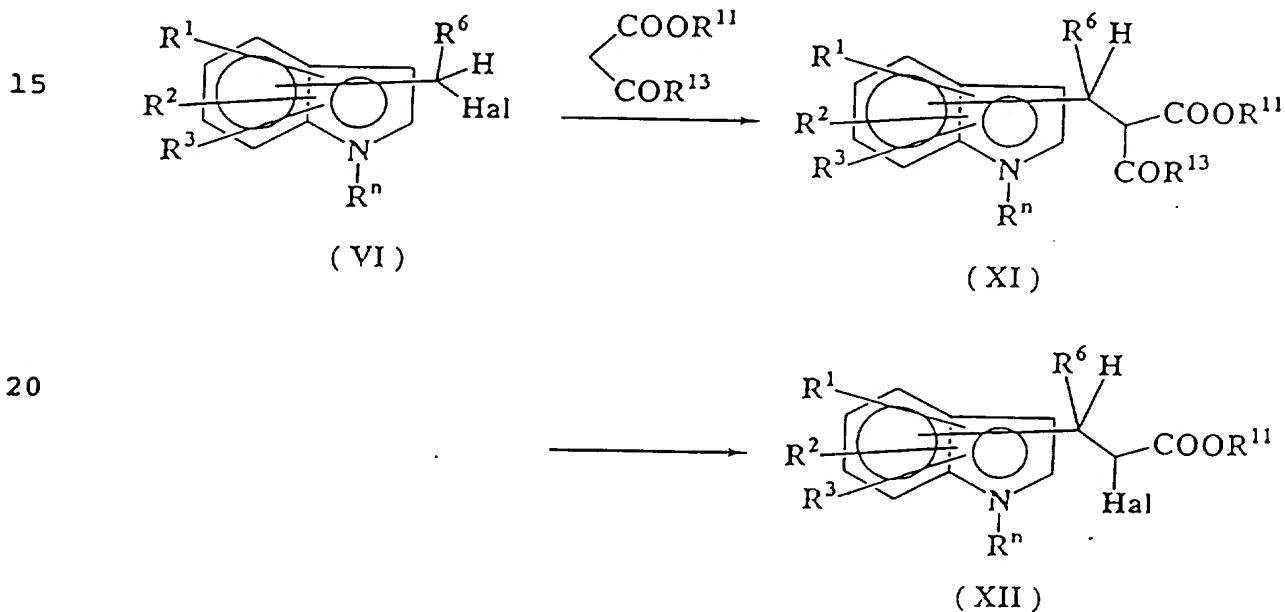
- 122 -

(wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^n$  are as defined above).

The formylated product (II) can be obtained by reducing a cyano group of an indole of the formula (XIII). This step can be conducted by using an appropriate reducing agent (such as Raney nickel, nickel, sodium aluminum hydride, sodium triethoxyaluminum hydride, diisobutylaluminum hydride and tin chloride (II)).

An example of reducing an indole (XIII) by using Raney nickel is described in Japanese Unexamined Patent Publication No. 151172/1986.

Method for preparing intermediate (XII)



25 (wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^6$ ,  $R^{11}$ ,  $Z$  and  $Hal$  are as defined above, and  $R^{13}$  is  $OR^{11}$  ( $R^{11}$  is as defined above) or  $C_1-C_3$  alkyl such as methyl, ethyl, n-propyl and i-propyl).

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A halocarboxylic acid ester of the formula (XII) can be obtained by reacting a halomethylindole of the formula (VI) with a malonic acid ester or a lower acylacetic acid ester by a well known method to obtain a compound of the 5 formula (XI) and halogenating the compound of the formula (XI) thus obtained.

The halomethylindole of the formula (VI) can be synthesized by the method disclosed in "Org. Prep. Proced. Int." vol. 25, P249 (1993). Thus, the 10 halomethylindole of the formula (VI) can be obtained by halogenating a hydroxymethylindole of the formula (III) with an appropriate halogenating agent (such as  $\text{SOCl}_2$ ,  $\text{POCl}_3$ ,  $\text{PCl}_5$ ,  $\text{HCl}$ ,  $\text{SnCl}_4$ ,  $\text{HBr}$ ,  $\text{PBr}_3$ ,  $\text{Br}_2$ ,  $\text{POBr}_3$ , methanesulfonic acid chloride, p-toluenesulfonic acid 15 chloride, N-bromosuccinimide-triphenylphosphine and N-chlorosuccinimide-triphenylphosphine).

Among compounds of the formula (XI), a compound wherein  $\text{R}^{13}$  is  $\text{C}_1\text{-C}_3$  alkyl, can be obtained by reacting a halomethylindole of the formula (VI) with a lower 20 acylacetic acid ester such as methyl acetoacetate or ethyl acetoacetate in the presence of an appropriate base (such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium amide, potassium amide, diisopropylamide, butyl lithium, metallic sodium, 25 potassium carbonate, sodium hydride, potassium hydride and calcium hydride) in accordance with the method disclosed in "J. Amer. Chem. Soc." vol 64, P435 (1942).

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Among compounds of the formula (XII), a compound wherein R<sup>13</sup> is OR<sup>11</sup>, can be obtained by reacting a halomethylindole of the formula (VI) with a malonic acid ester such as diethyl malonate or di-t-butyl malonate in 5 the presence of such a base as mentioned above, in accordance with the method disclosed in "J. Amer. Chem. Soc." vol 74, P831 (1952).

The step for preparing a compound of the formula (XII) is conducted by using an appropriate halogenating 10 agent (such as bromine or N-chlorosuccinimide) in the presence of an appropriate base (such as potassium hydroxide, sodium methoxide or potassium carbonate) in accordance with the method disclosed in "J. Amer. Chem. Soc." vol 71, P3107 (1949) or "Tetrahedron Letters" vol. 15 28, P5505 (1987).

Also, a compound of the formula (XII) can be obtained by reacting a halomethylindole of the formula (VI) with a diazoacetic acid ester in the presence of a copper catalyst in accordance with the method disclosed in "Zur. 20 Russ. Fiz-Chim." vol. 21, P851 (1951).

Among the above-mentioned compounds (II), (III), (VII) and (IX), the compound having a carbon functional group as R<sup>1</sup> is a novel compound and is useful as an intermediate for preparing the compound of the formula 25 (I).

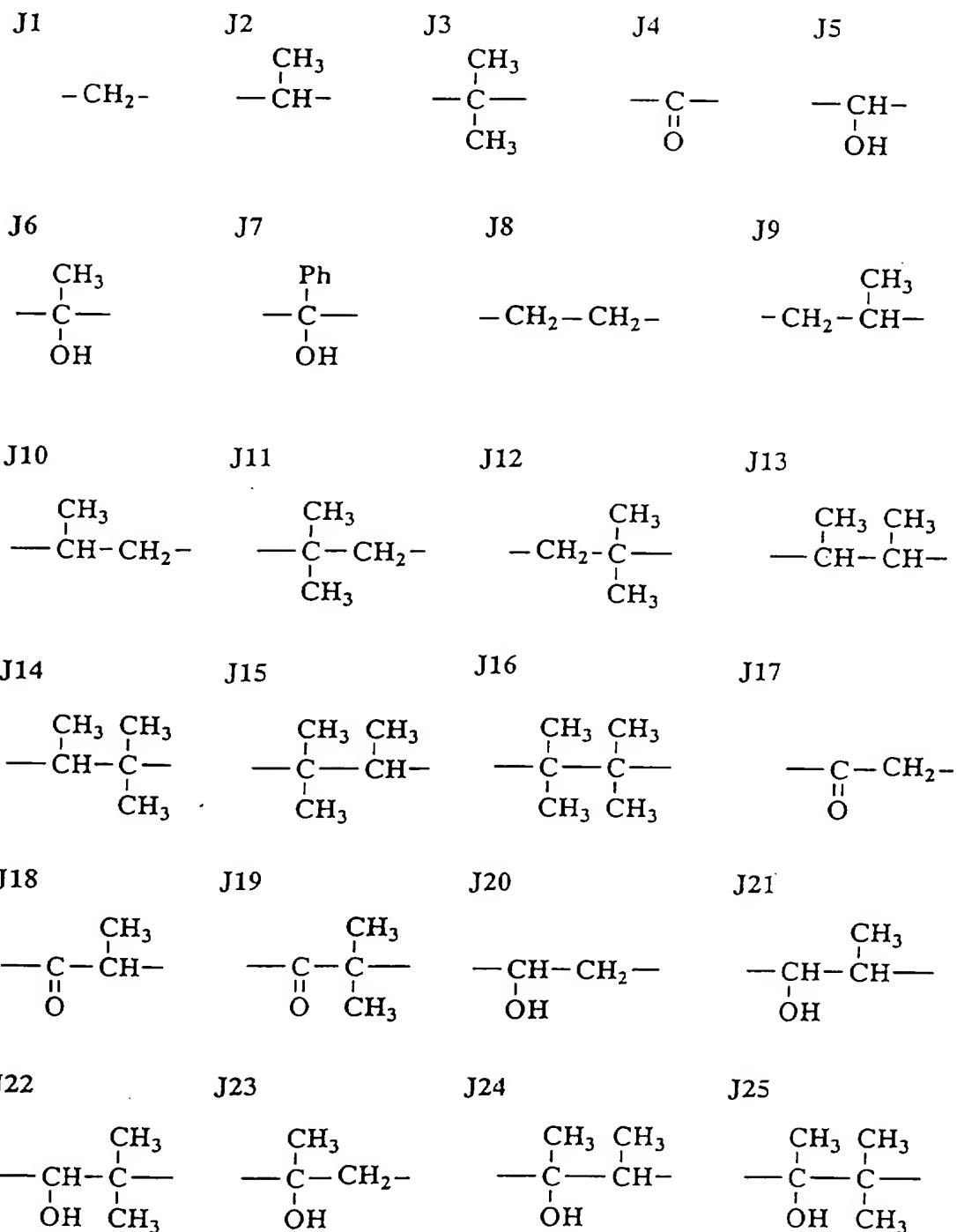
Examples of the compound of the present invention are illustrated as compounds of the formulas (I-1) and (I-2)

- 125 -

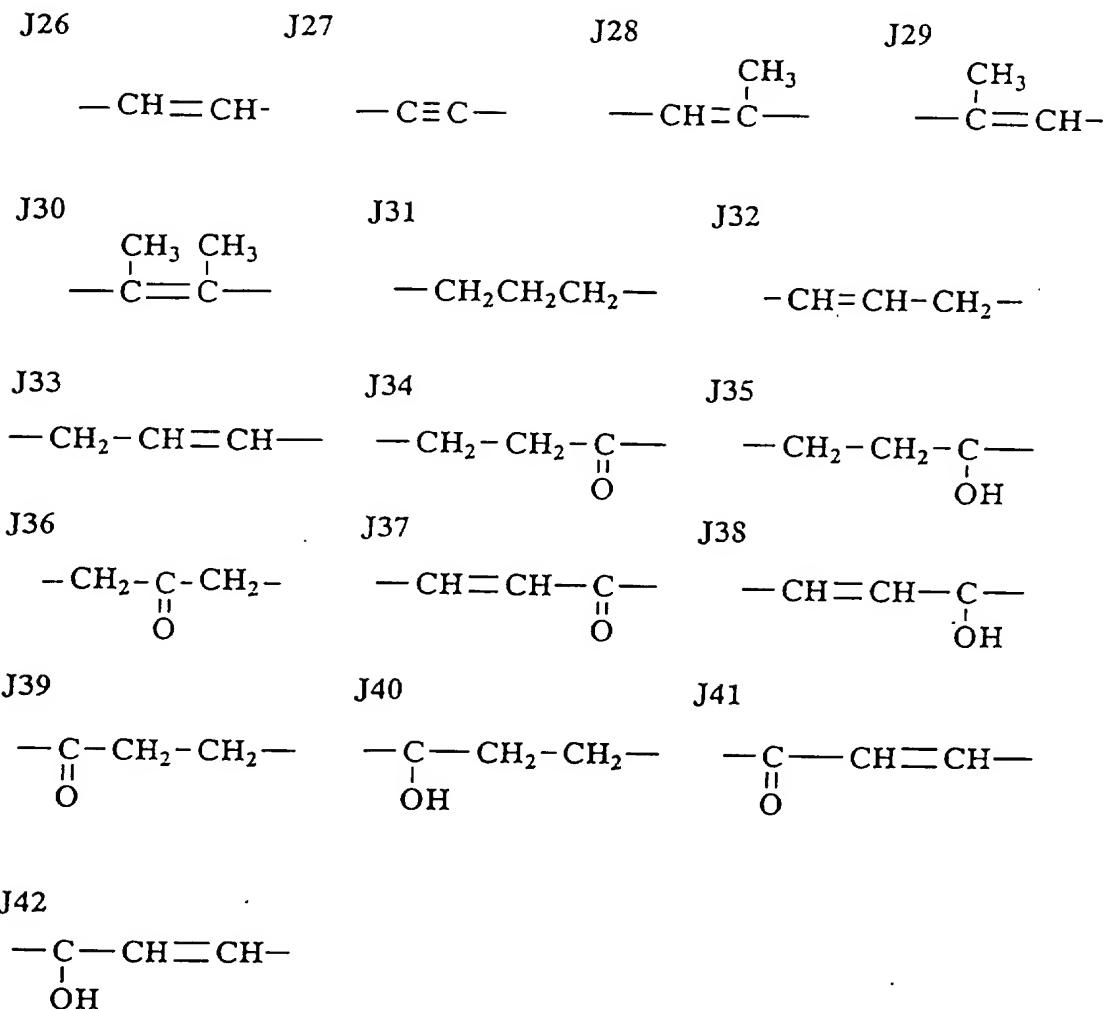
in Tables 1 to 10. Also, the above described salts derived by reacting basic nitrogen at the 3-position of the thiazolidine ring by means of a well known method are also the compounds of the present invention.

5 In the Tables, Me is a methyl group; Et is an ethyl group; Pr is a propyl group; Bu is a butyl group; Pen is a pentyl group; Hex is a hexyl group; Hep is a heptyl group; Ph is a phenyl group; n means "normal"; i means "iso"; s means "secondary"; t means "tertiary"; and c 10 means "cyclo". Also, Q1 to Q317 and J1 to J42 represent the following substituents.

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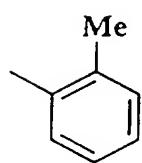


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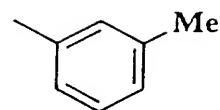


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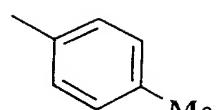
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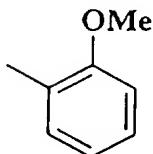
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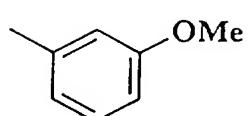
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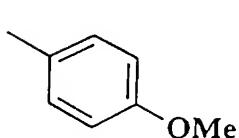
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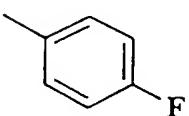
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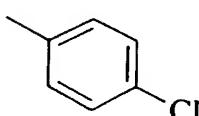
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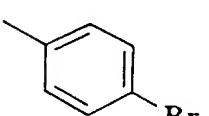
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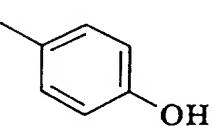
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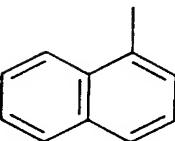
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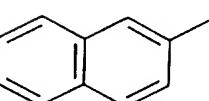
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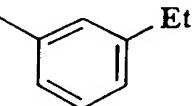
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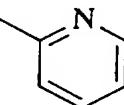
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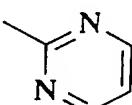
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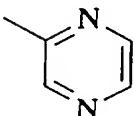
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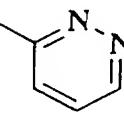
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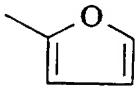
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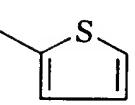
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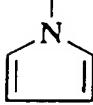
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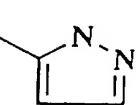
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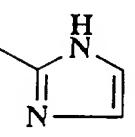
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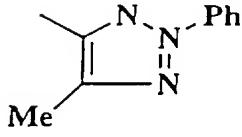
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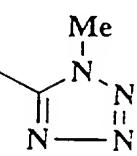
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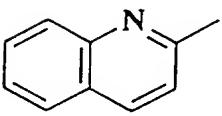
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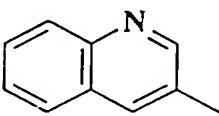
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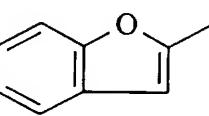
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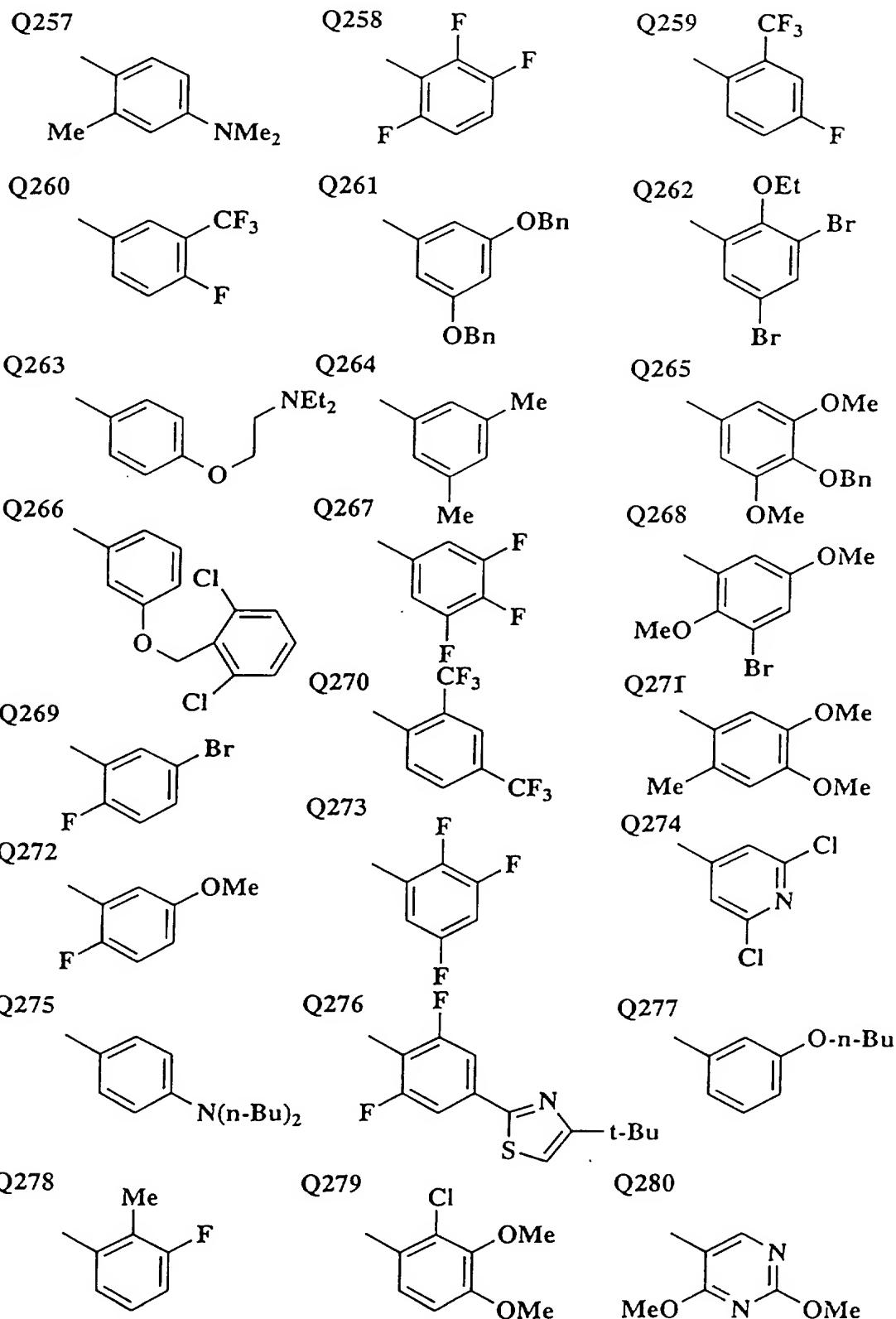
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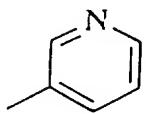


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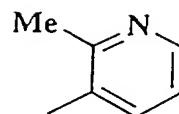


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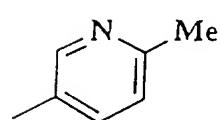
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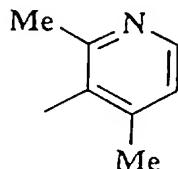
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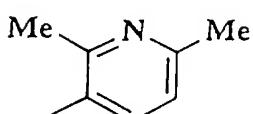
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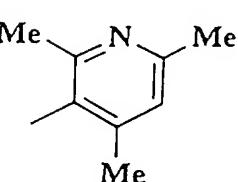
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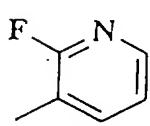
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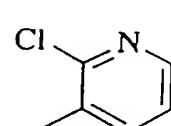
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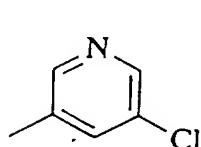
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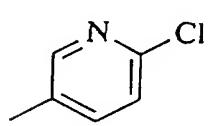
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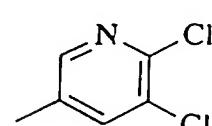
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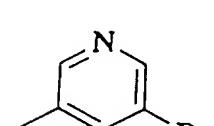
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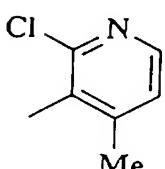
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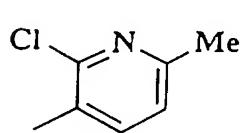
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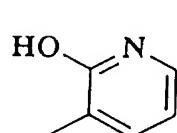
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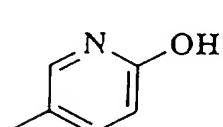
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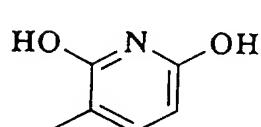
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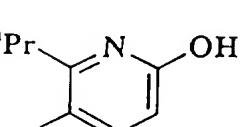
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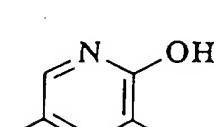
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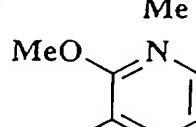
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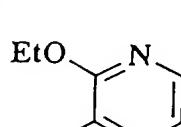
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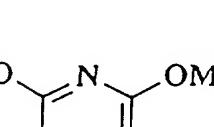
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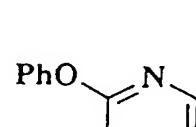
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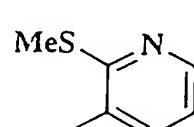
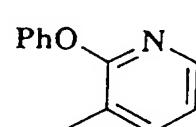
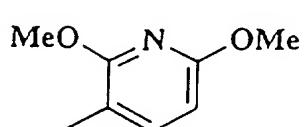
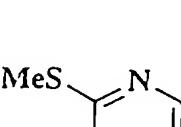
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Q71

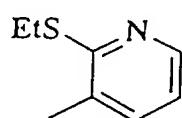


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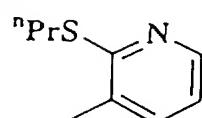


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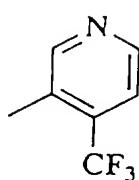
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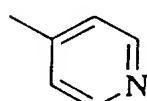
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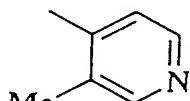
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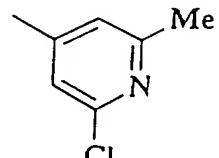
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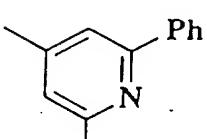
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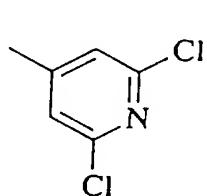
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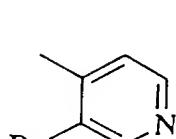
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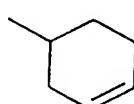
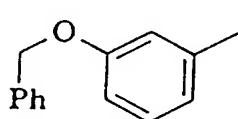
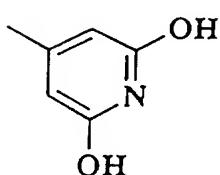
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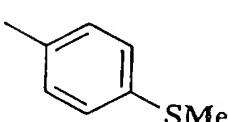
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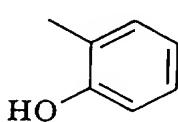
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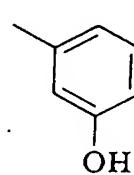
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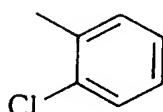
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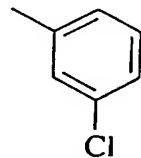
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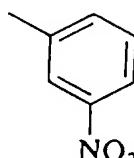
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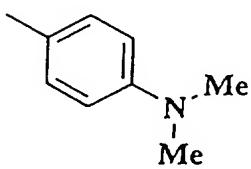
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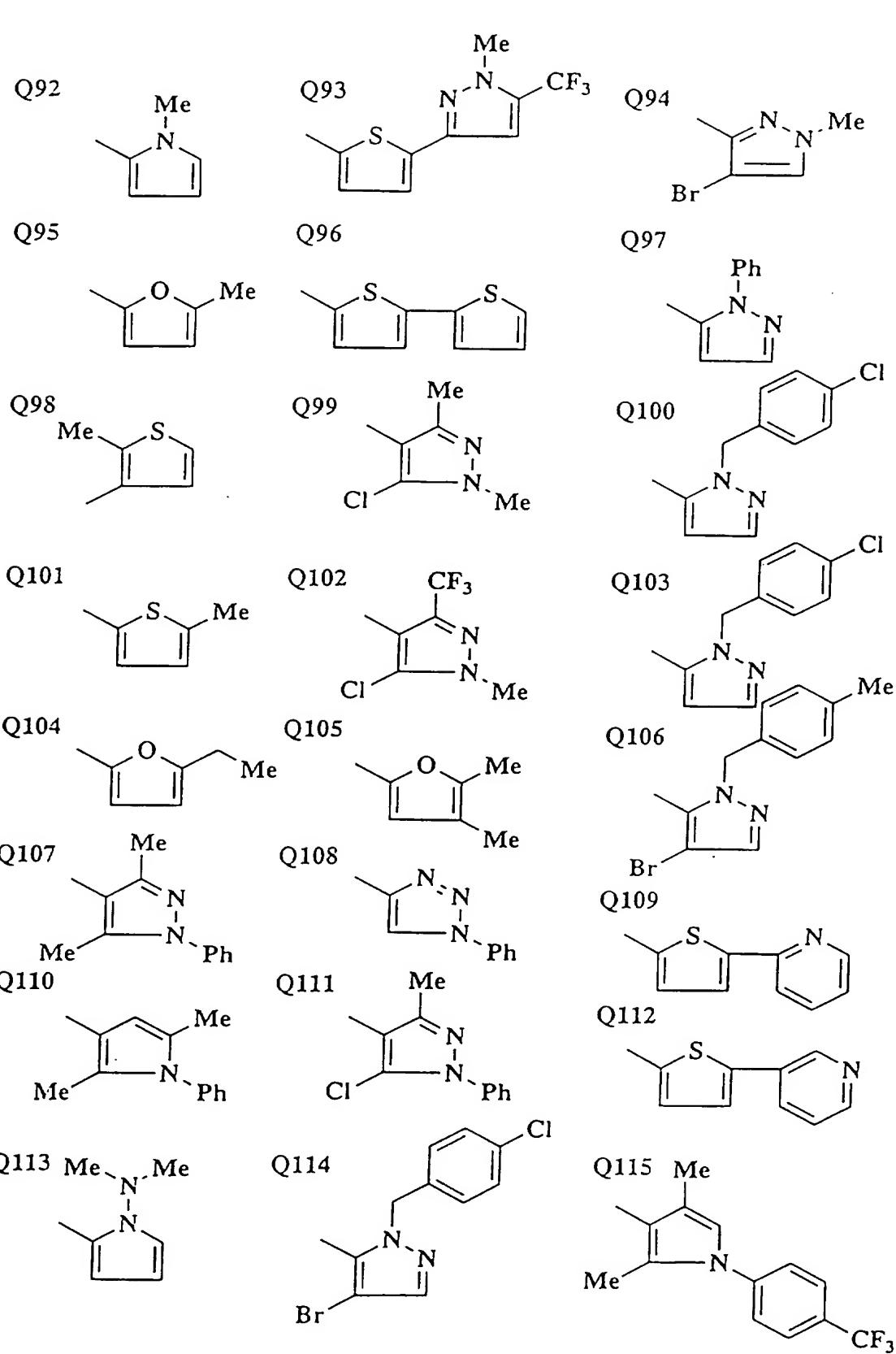
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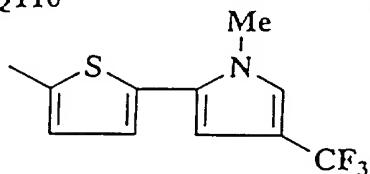


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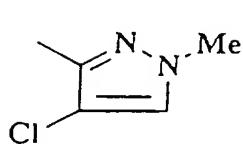


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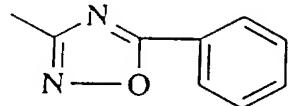
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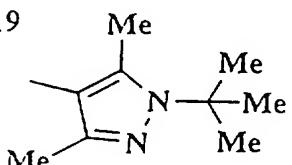
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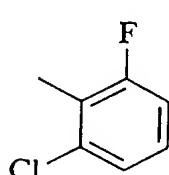
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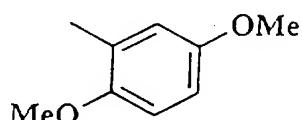
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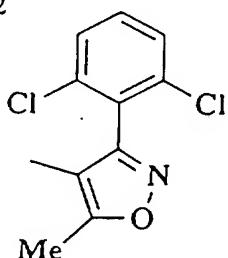
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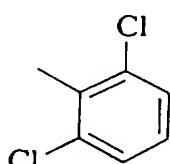
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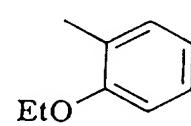
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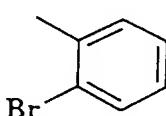
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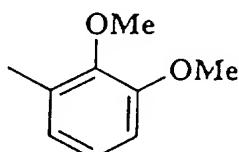
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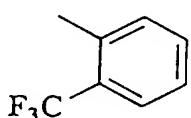
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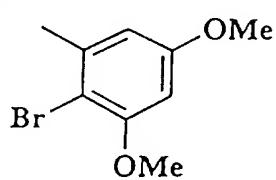
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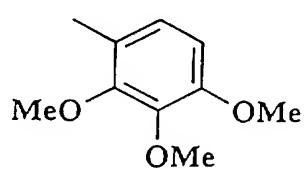
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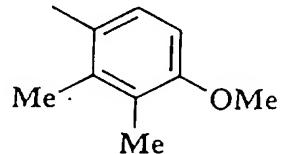
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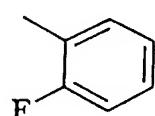
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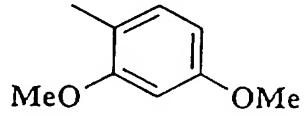
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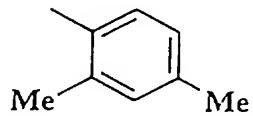
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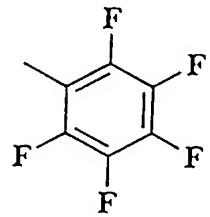
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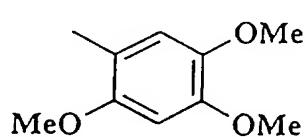
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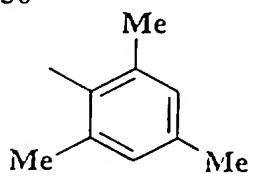
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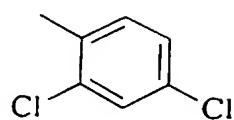


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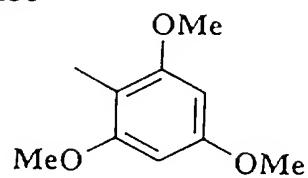


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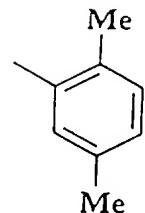
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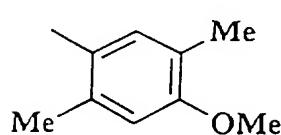
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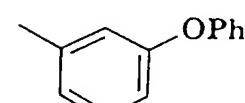
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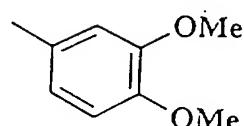
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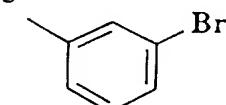
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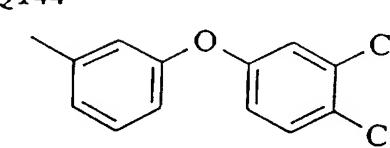
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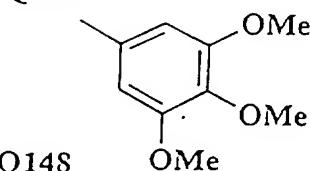
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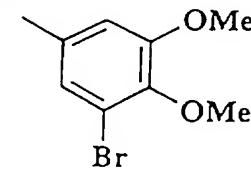
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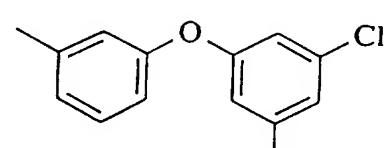
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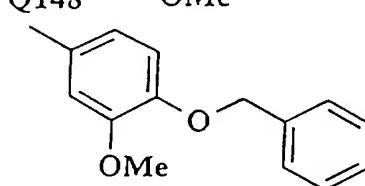
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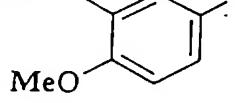
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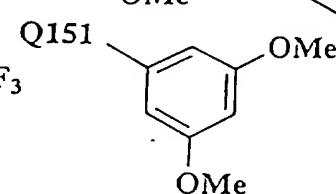
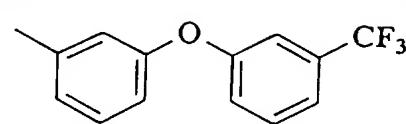
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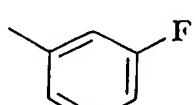
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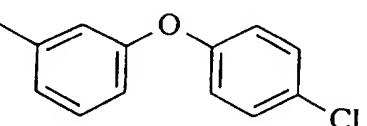
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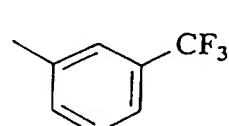
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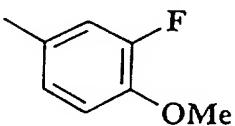
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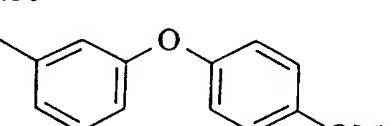
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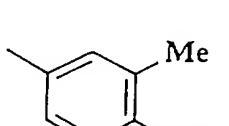
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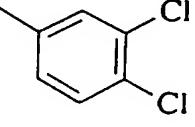
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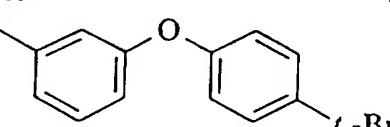
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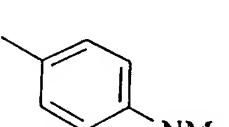
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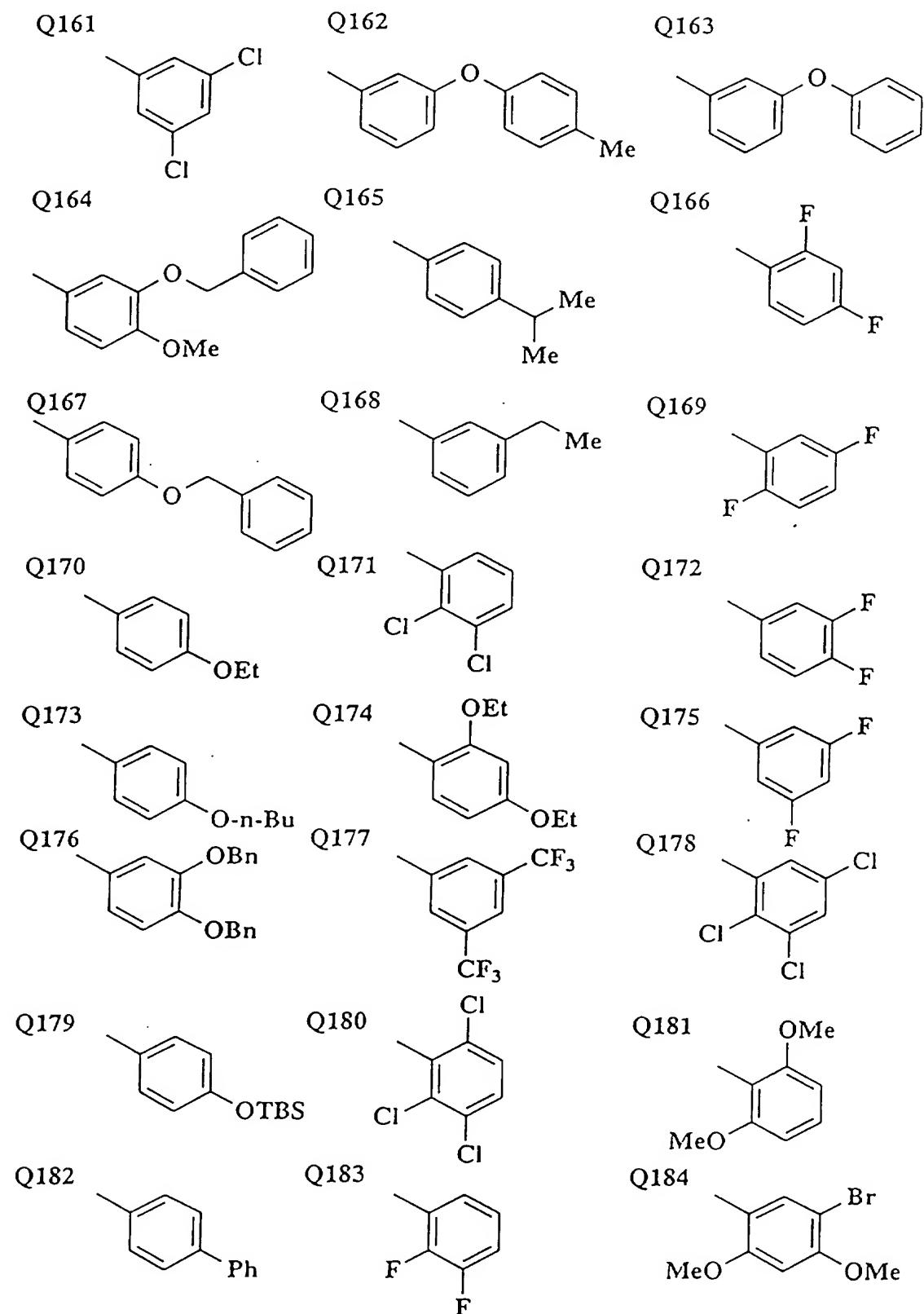
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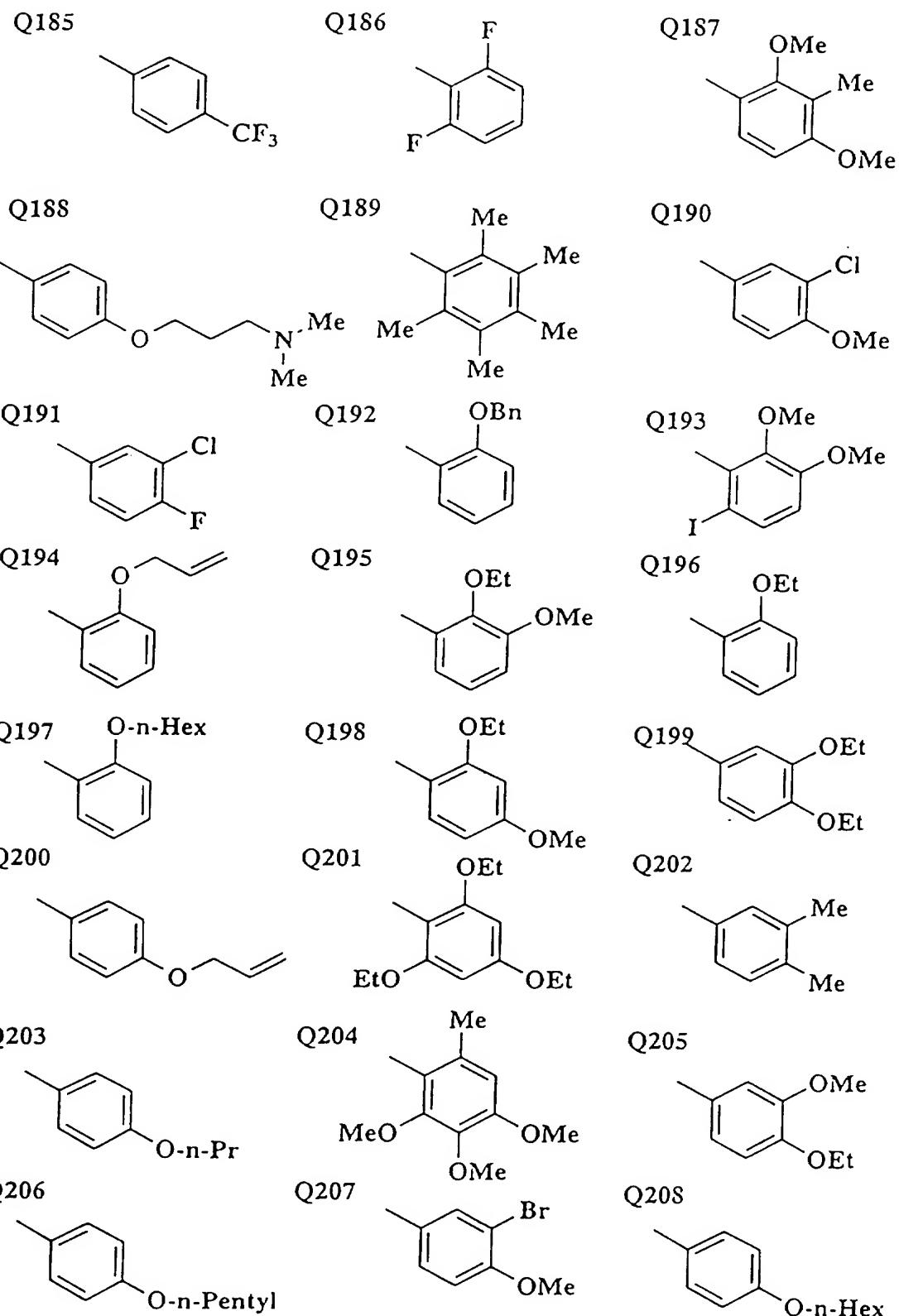


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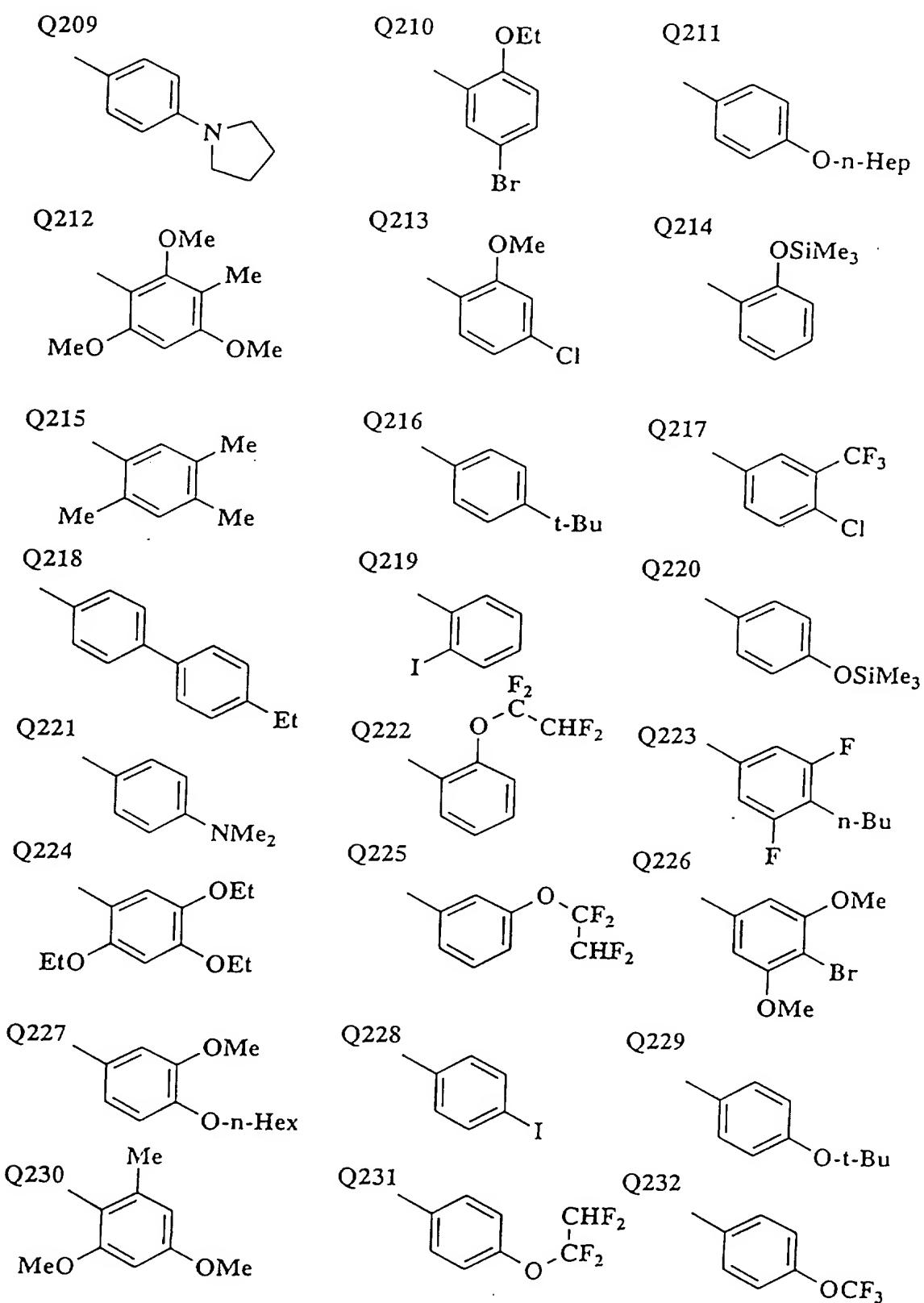


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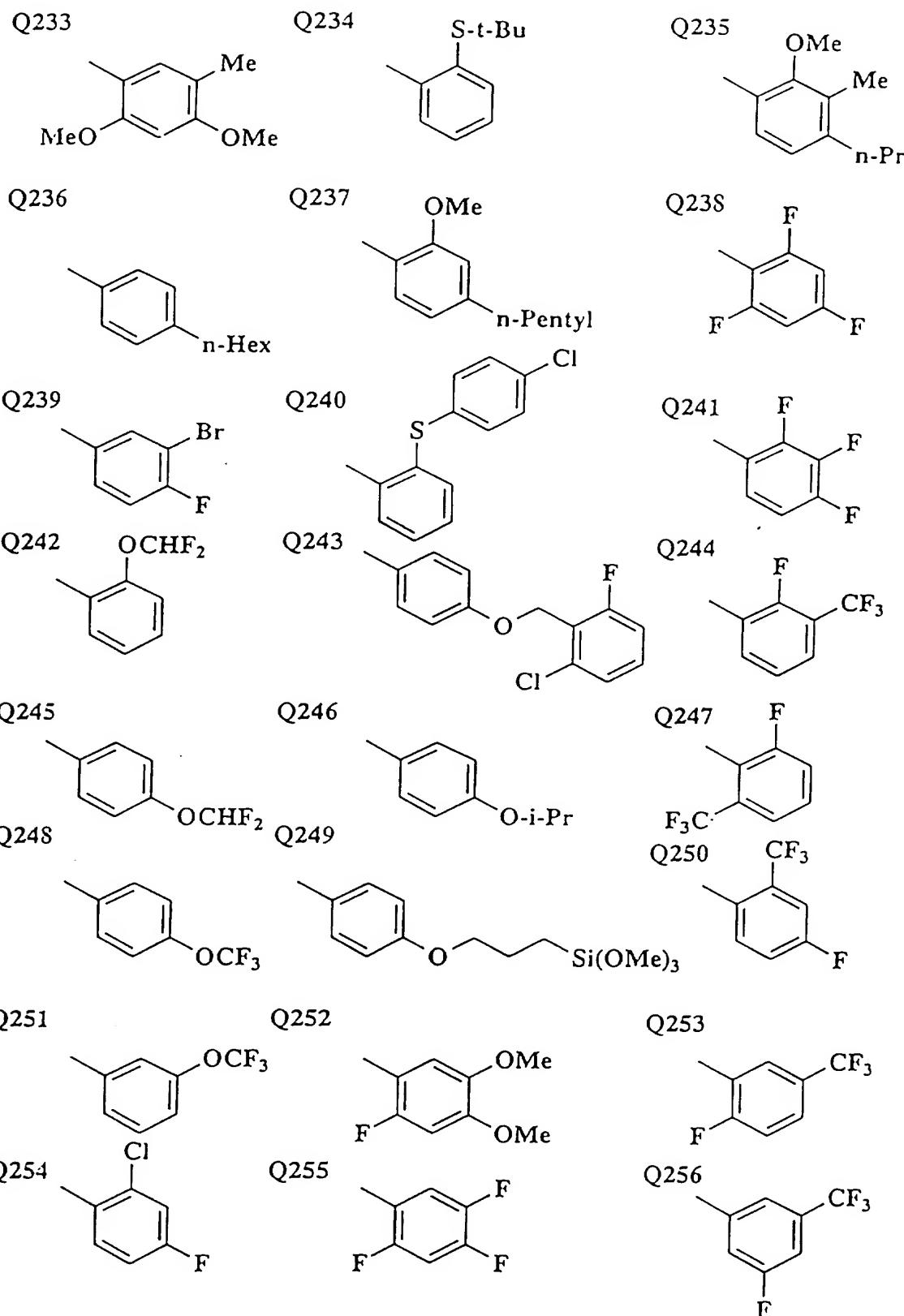




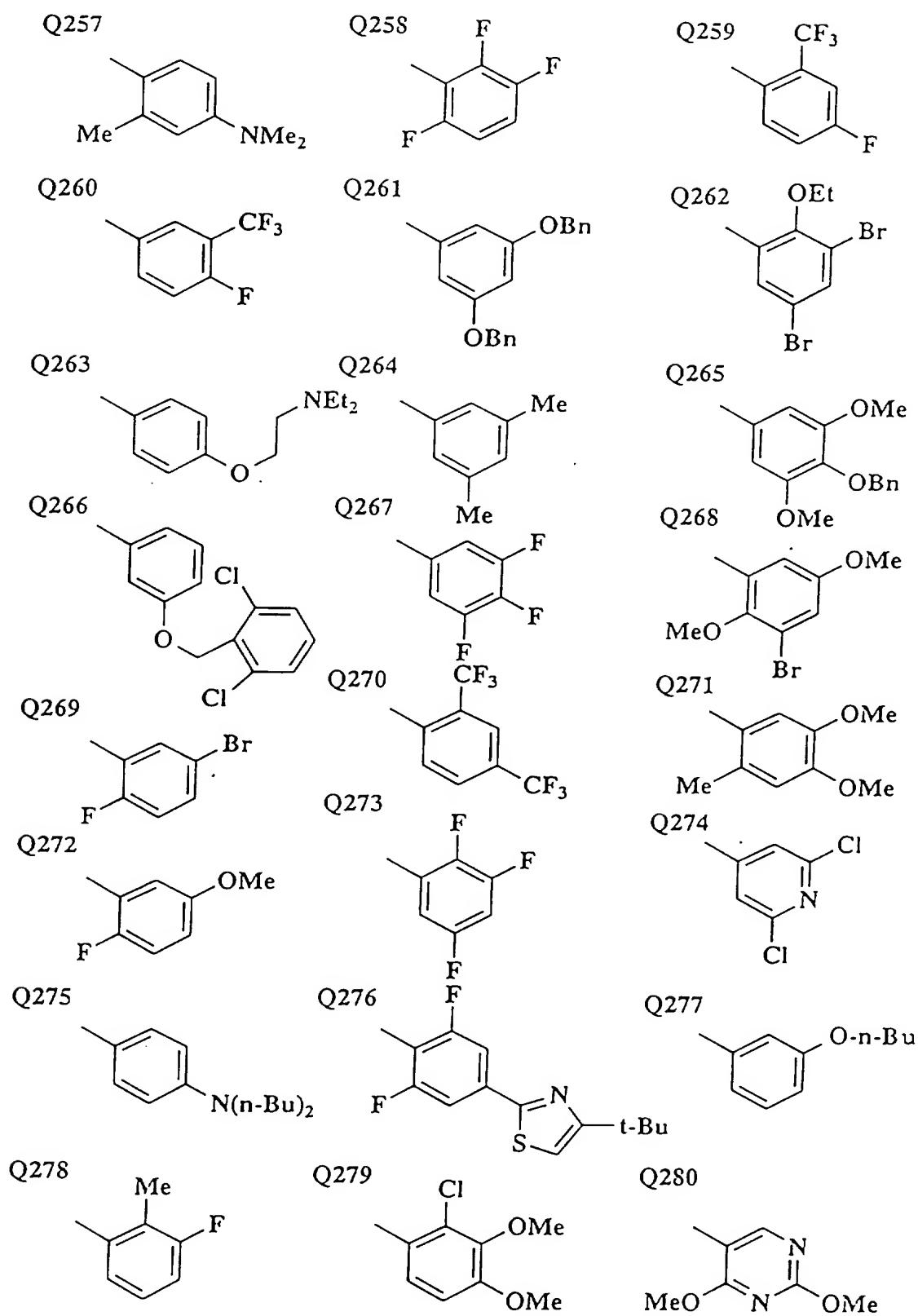
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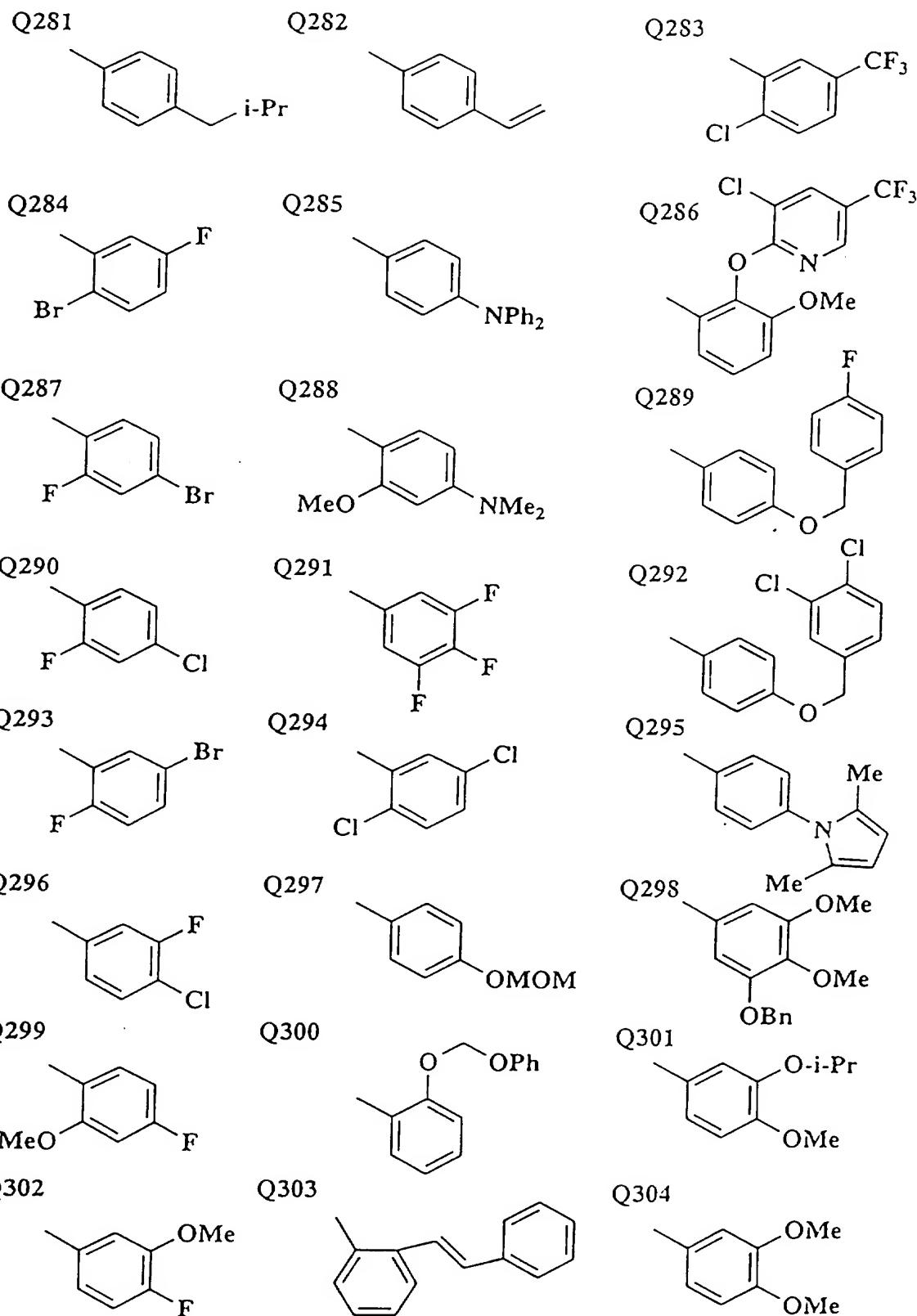
- 138 -



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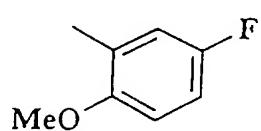


- 140 -

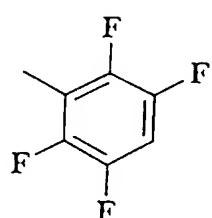


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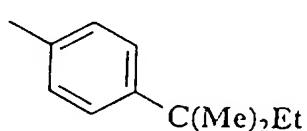
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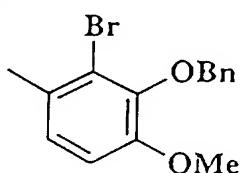
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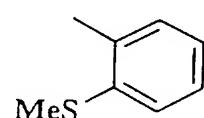
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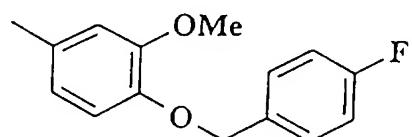
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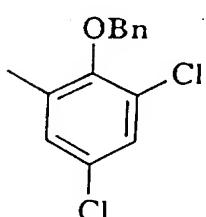
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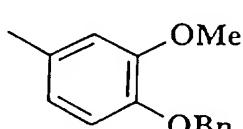
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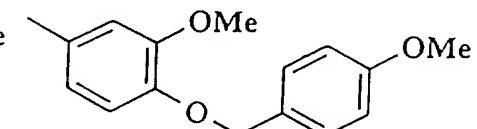
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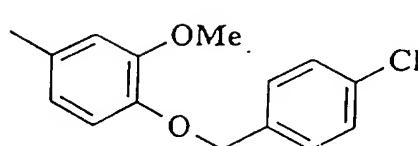
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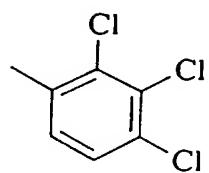
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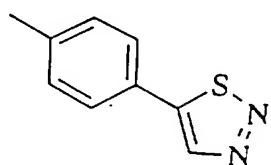
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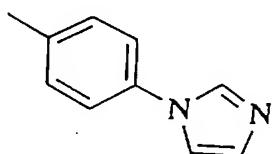
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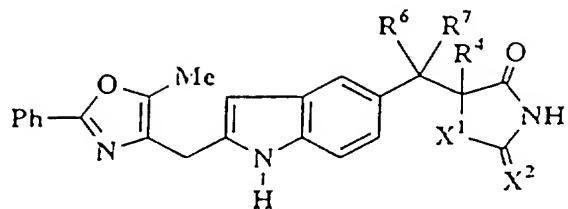
Q316



Q317



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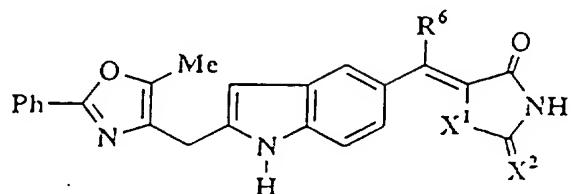


5 In the above formula,  $X^1$ ,  $X^2$ ,  $R^4$ ,  $R^6$  and  $R^7$  are selected from the following Table 1.

Table 1

	$X^1$	$X^2$	$R^4$	$R^6$	$R^7$
10	S	O	H	H	H
	S	S	H	H	H
	O	S	H	H	H
	O	O	H	H	H
15	S	O	Me	H	H
	S	S	Me	H	H
	O	S	Me	H	H
	O	O	Me	H	H
	S	O	H	H	Me
20	S	S	H	H	Me
	O	S	H	H	Me
	O	O	H	H	Me
	S	O	Me	H	Me
	S	S	Me	H	Me
25	O	S	Me	H	Me
	O	O	Me	H	Me

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5 In the above formula,  $X^1$ ,  $X^2$  and  $R^6$  are selected from the following Table 2.

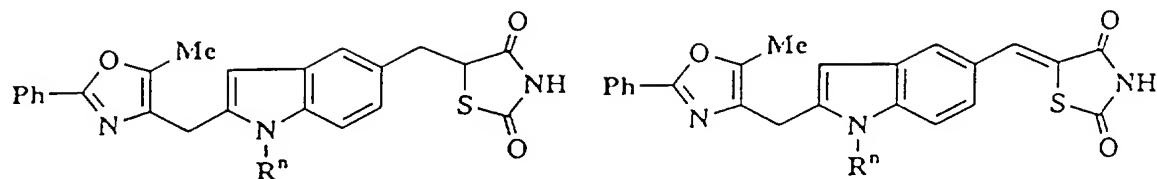
Table 2

	$X^1$	$X^2$	$R^6$
10	S	O	H
	S	S	H
	O	S	H
	O	O	H
15	S	O	Me
	S	S	Me
	O	S	Me
	O	O	Me

---

S	O	H	
S	S	H	
O	S	H	
O	O	H	
15	S	O	Me
	S	S	Me
	O	S	Me
	O	O	Me

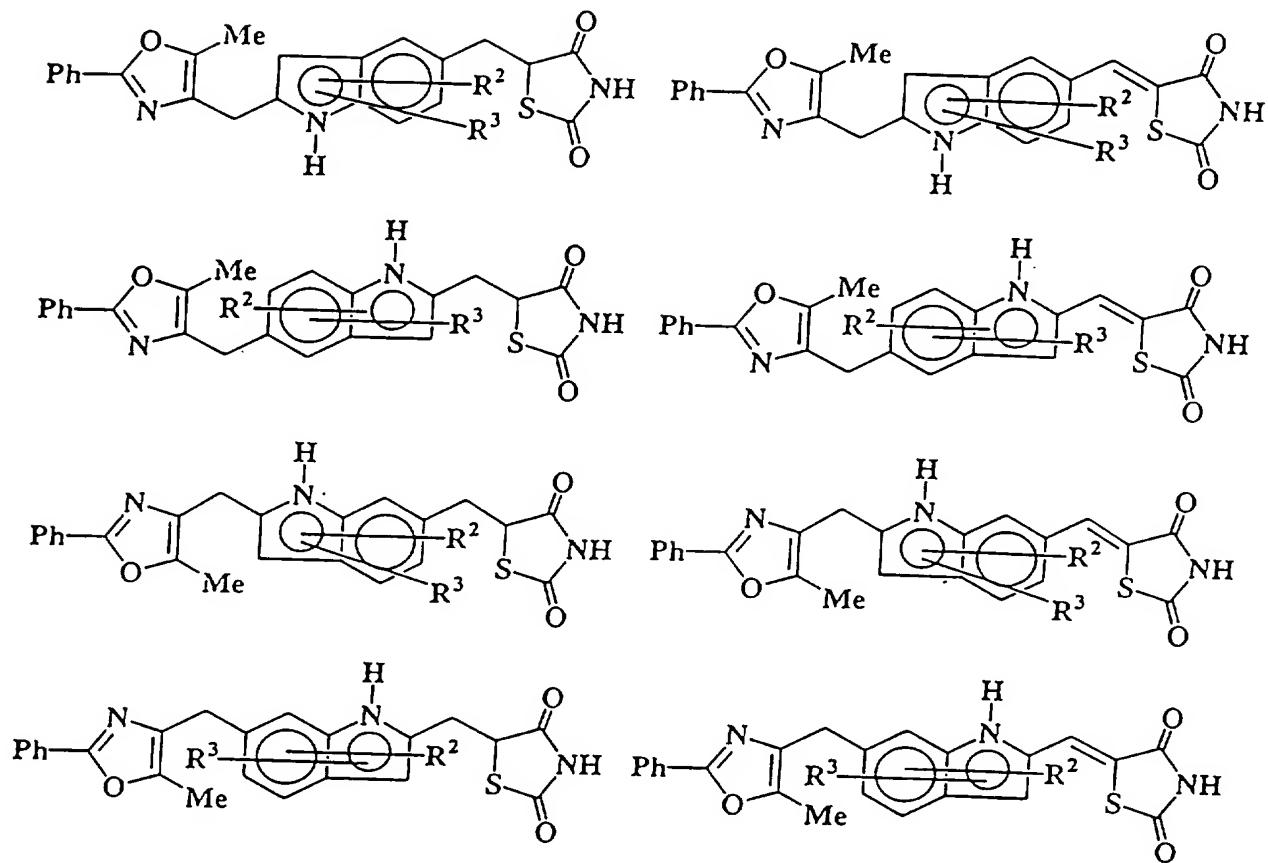
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5 In the above formula,  $R^n$  is selected from the following Table 3.

Table 3

	$R^n$	$R^n$
10		
	H	benzoyl
	Me	methoxycarbonyl
	<sup>n</sup> Bu	benzyloxycarbonyl
	<sup>n</sup> Hex	methylcarbamoyl
15	<sup>c</sup> Pr	phenylcarbamoyl
	<sup>c</sup> Hex	methoxy
	methoxymethyl	n-butoxy
	benzyloxymethyl	n-hexyloxy
	dimethoxyaminomethyl	methoxymethyloxy
20	acetamidemethyl	triisopropylsilyl
	methylthiomethyl	t-butyldiphenylsilyl
	carboxyl	methanesulfonyl
	formyl	benzenesulfonyl
	acetyl	
25		



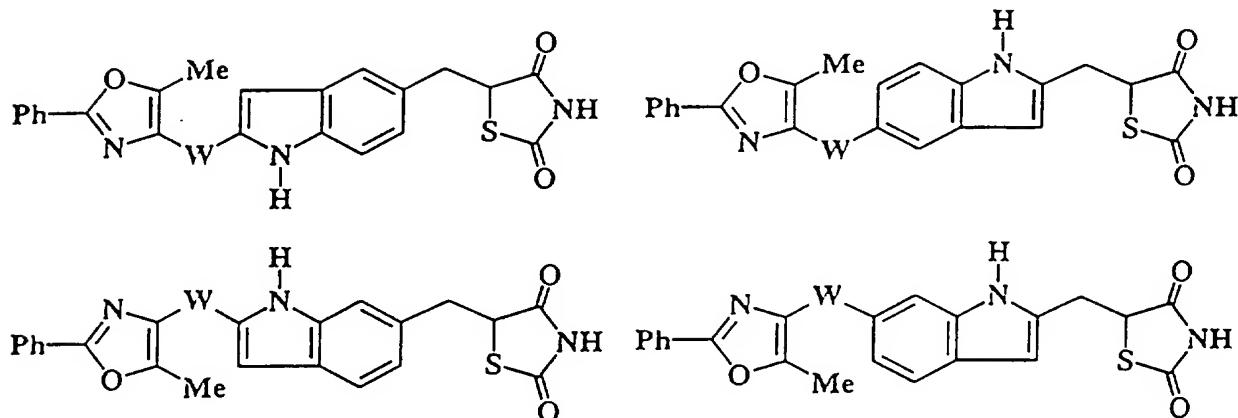
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In the above formula, R<sup>2</sup> and R<sup>3</sup> are selected from the following Table 4.

Table 4

	R <sup>2</sup>	R <sup>3</sup>
5	3-OH	H
	4-OH	H
	6-OH	H
	7-OH	H
	3-Me	H
	3-MeO	H
10	3-PhCH <sub>2</sub> O	H
	3-Ph	H
15	3-Cl	H

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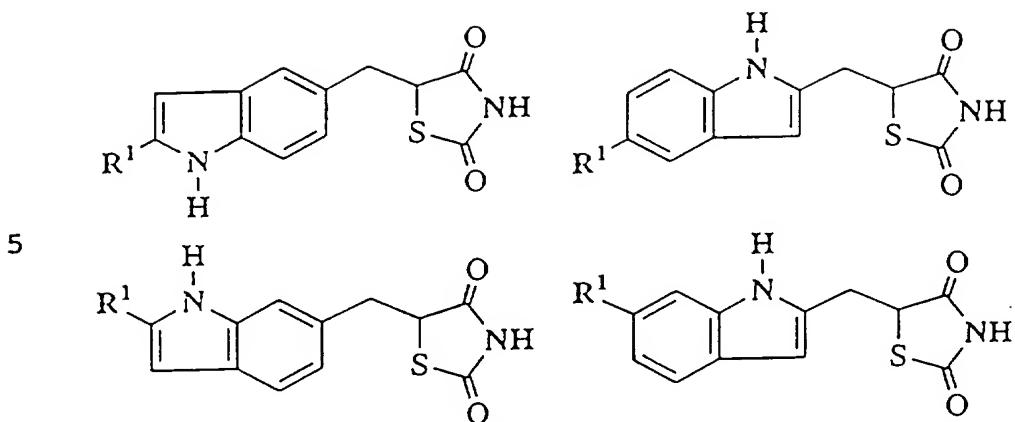


10 In the above formula, W is selected from the  
following Table 5.

Table 5

	W	W	W	W
15	J1	J12	J23	J34
	J2	J13	J24	J35
	J3	J14	J25	J36
	J4	J15	J26	J37
20	J5	J16	J27	J38
	J6	J17	J28	J39
	J7	J18	J29	J40
	J8	J19	J30	J41
	J9	J20	J31	J42
25	J10	J21	J32	
	J11	J22	J33	

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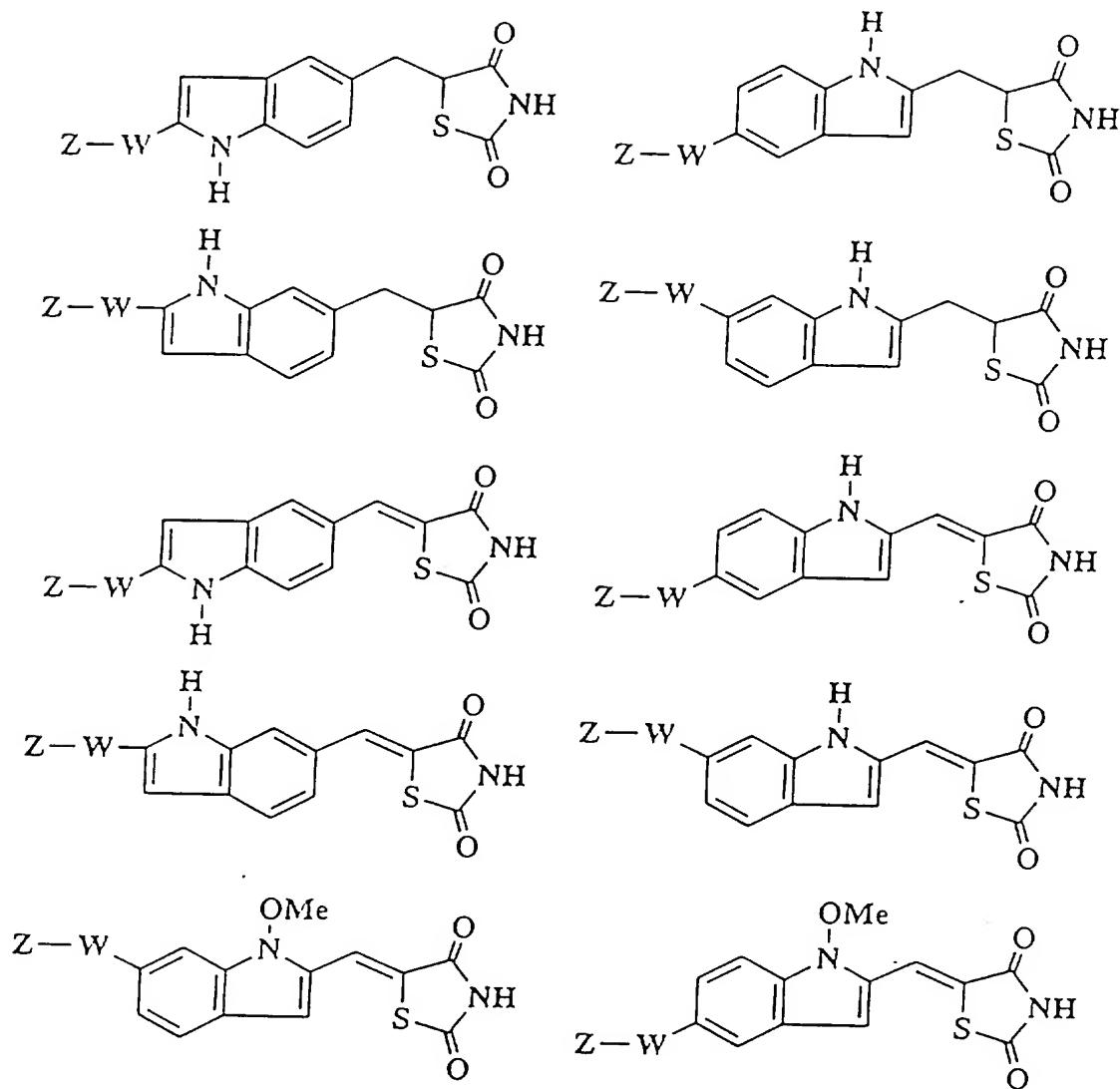


10 In the above formula, R¹ is selected from the following Table 6.

Table 6

	R¹
15	n-hexyl
	1-hexenyl
	1-hexynyl
	n-hexyloxy
	2-hexenyloxy
20	n-hexylthio
	n-hexylamino
	N-methyl-N-n-hexylamino

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In the above formula, Z and W are selected from the following Tables 7 to 22.

Table 7

5	Z	W	Z	W	Z	W	Z	W
	Q1	J1	Q21	J1	Q41	J1	Q61	J1
	Q2	J1	Q22	J1	Q42	J1	Q62	J1
	Q3	J1	Q23	J1	Q43	J1	Q63	J1
10	Q4	J1	Q24	J1	Q44	J1	Q64	J1
	Q5	J1	Q25	J1	Q45	J1	Q65	J1
	Q6	J1	Q26	J1	Q46	J1	Q66	J1
	Q7	J1	Q27	J1	Q47	J1	Q67	J1
	Q8	J1	Q28	J1	Q48	J1	Q68	J1
15	Q9	J1	Q29	J1	Q49	J1	Q69	J1
	Q10	J1	Q30	J1	Q50	J1	Q70	J1
	Q11	J1	Q31	J1	Q51	J1	Q71	J1
	Q12	J1	Q32	J1	Q52	J1	Q72	J1
	Q13	J1	Q33	J1	Q53	J1	Q73	J1
20	Q14	J1	Q34	J1	Q54	J1	Q74	J1
	Q15	J1	Q35	J1	Q55	J1	Q75	J1
	Q16	J1	Q36	J1	Q56	J1	Q76	J1
	Q17	J1	Q37	J1	Q57	J1	Q77	J1
	Q18	J1	Q38	J1	Q58	J1	Q78	J1
25	Q19	J1	Q39	J1	Q59	J1	Q79	J1
	Q20	J1	Q40	J1	Q60	J1	Q80	J1

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Table 8

	Z	W	Z	W	Z	W	Z	W
5	Q81	J1	Q101	J1	Q121	J1	Q141	J1
	Q82	J1	Q102	J1	Q122	J1	Q142	J1
	Q83	J1	Q103	J1	Q123	J1	Q143	J1
	Q84	J1	Q104	J1	Q124	J1	Q144	J1
	Q85	J1	Q105	J1	Q125	J1	Q145	J1
10	Q86	J1	Q106	J1	Q126	J1	Q146	J1
	Q87	J1	Q107	J1	Q127	J1	Q147	J1
	Q88	J1	Q108	J1	Q128	J1	Q148	J1
	Q89	J1	Q109	J1	Q129	J1	Q149	J1
	Q90	J1	Q110	J1	Q130	J1	Q150	J1
15	Q91	J1	Q111	J1	Q131	J1	Q151	J1
	Q92	J1	Q112	J1	Q132	J1	Q152	J1
	Q93	J1	Q113	J1	Q133	J1	Q153	J1
	Q94	J1	Q114	J1	Q134	J1	Q154	J1
	Q95	J1	Q115	J1	Q135	J1	Q155	J1
20	Q96	J1	Q116	J1	Q136	J1	Q156	J1
	Q97	J1	Q117	J1	Q137	J1	Q157	J1
	Q98	J1	Q118	J1	Q138	J1	Q158	J1
	Q99	J1	Q119	J1	Q139	J1	Q159	J1
	Q100	J1	Q120	J1	Q140	J1	Q160	J1

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Table 9

	Z	W	Z	W	Z	W	Z	W
5	Q161 J1	Q181 J1	Q201 J1	Q221 J1				
	Q162 J1	Q182 J1	Q202 J1	Q222 J1				
	Q163 J1	Q183 J1	Q203 J1	Q223 J1				
	Q164 J1	Q184 J1	Q204 J1	Q224 J1				
	Q165 J1	Q185 J1	Q205 J1	Q225 J1				
10	Q166 J1	Q186 J1	Q206 J1	Q226 J1				
	Q167 J1	Q187 J1	Q207 J1	Q227 J1				
	Q168 J1	Q188 J1	Q208 J1	Q228 J1				
	Q169 J1	Q189 J1	Q209 J1	Q229 J1				
	Q170 J1	Q190 J1	Q210 J1	Q230 J1				
15	Q171 J1	Q191 J1	Q211 J1	Q231 J1				
	Q172 J1	Q192 J1	Q212 J1	Q232 J1				
	Q173 J1	Q193 J1	Q213 J1	Q233 J1				
	Q174 J1	Q194 J1	Q214 J1	Q234 J1				
	Q175 J1	Q195 J1	Q215 J1	Q235 J1				
20	Q176 J1	Q196 J1	Q216 J1	Q236 J1				
	Q177 J1	Q197 J1	Q217 J1	Q237 J1				
	Q178 J1	Q198 J1	Q218 J1	Q238 J1				
	Q179 J1	Q199 J1	Q219 J1	Q239 J1				
	Q180 J1	Q200 J1	Q220 J1	Q240 J1				

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Table 10

	Z	W	Z	W	Z	W	Z	W
5	Q241	J1	Q261	J1	Q281	J1	Q301	J1
	Q242	J1	Q262	J1	Q282	J1	Q302	J1
	Q243	J1	Q263	J1	Q283	J1	Q303	J1
	Q244	J1	Q264	J1	Q284	J1	Q304	J1
	Q245	J1	Q265	J1	Q285	J1	Q305	J1
10	Q246	J1	Q266	J1	Q286	J1	Q306	J1
	Q247	J1	Q267	J1	Q287	J1	Q307	J1
	Q248	J1	Q268	J1	Q288	J1	Q308	J1
	Q249	J1	Q269	J1	Q289	J1	Q309	J1
	Q250	J1	Q270	J1	Q290	J1	Q310	J1
15	Q251	J1	Q271	J1	Q291	J1	Q311	J1
	Q252	J1	Q272	J1	Q292	J1	Q312	J1
	Q253	J1	Q273	J1	Q293	J1	Q313	J1
	Q254	J1	Q274	J1	Q294	J1	Q314	J1
	Q255	J1	Q275	J1	Q295	J1	Q315	J1
20	Q256	J1	Q276	J1	Q296	J1	Q316	J1
	Q257	J1	Q277	J1	Q297	J1	Q317	J1
	Q258	J1	Q278	J1	Q298	J1		
	Q259	J1	Q279	J1	Q299	J1		
	Q260	J1	Q280	J1	Q300	J1		

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Table 11

	Z	W	Z	W	Z	W	Z	W
5	Q1	J2	Q21	J2	Q41	J2	Q61	J2
	Q2	J2	Q22	J2	Q42	J2	Q62	J2
	Q3	J2	Q23	J2	Q43	J2	Q63	J2
	Q4	J2	Q24	J2	Q44	J2	Q64	J2
	Q5	J2	Q25	J2	Q45	J2	Q65	J2
10	Q6	J2	Q26	J2	Q46	J2	Q66	J2
	Q7	J2	Q27	J2	Q47	J2	Q67	J2
	Q8	J2	Q28	J2	Q48	J2	Q68	J2
	Q9	J2	Q29	J2	Q49	J2	Q69	J2
	Q10	J2	Q30	J2	Q50	J2	Q70	J2
15	Q11	J2	Q31	J2	Q51	J2	Q71	J2
	Q12	J2	Q32	J2	Q52	J2	Q72	J2
	Q13	J2	Q33	J2	Q53	J2	Q73	J2
	Q14	J2	Q34	J2	Q54	J2	Q74	J2
	Q15	J2	Q35	J2	Q55	J2	Q75	J2
20	Q16	J2	Q36	J2	Q56	J2	Q76	J2
	Q17	J2	Q37	J2	Q57	J2	Q77	J2
	Q18	J2	Q38	J2	Q58	J2	Q78	J2
	Q19	J2	Q39	J2	Q59	J2	Q79	J2
	Q20	J2	Q40	J2	Q60	J2	Q80	J2

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Table 12

	Z	W	Z	W	Z	W	Z	W
5	Q81 J2	Q101 J2	Q121 J2	Q141 J2				
	Q82 J2	Q102 J2	Q122 J2	Q142 J2				
	Q83 J2	Q103 J2	Q123 J2	Q143 J2				
	Q84 J2	Q104 J2	Q124 J2	Q144 J2				
	Q85 J2	Q105 J2	Q125 J2	Q145 J2				
10	Q86 J2	Q106 J2	Q126 J2	Q146 J2				
	Q87 J2	Q107 J2	Q127 J2	Q147 J2				
	Q88 J2	Q108 J2	Q128 J2	Q148 J2				
	Q89 J2	Q109 J2	Q129 J2	Q149 J2				
	Q90 J2	Q110 J2	Q130 J2	Q150 J2				
15	Q91 J2	Q111 J2	Q131 J2	Q151 J2				
	Q92 J2	Q112 J2	Q132 J2	Q152 J2				
	Q93 J2	Q113 J2	Q133 J2	Q153 J2				
	Q94 J2	Q114 J2	Q134 J2	Q154 J2				
	Q95 J2	Q115 J2	Q135 J2	Q155 J2				
20	Q96 J2	Q116 J2	Q136 J2	Q156 J2				
	Q97 J2	Q117 J2	Q137 J2	Q157 J2				
	Q98 J2	Q118 J2	Q138 J2	Q158 J2				
	Q99 J2	Q119 J2	Q139 J2	Q159 J2				
	Q100 J2	Q120 J2	Q140 J2	Q160 J2				

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Table 13

	Z	W	Z	W	Z	W	Z	W
5	Q161 J2	Q181 J2	Q201 J2	Q221 J2				
	Q162 J2	Q182 J2	Q202 J2	Q222 J2				
	Q163 J2	Q183 J2	Q203 J2	Q223 J2				
	Q164 J2	Q184 J2	Q204 J2	Q224 J2				
	Q165 J2	Q185 J2	Q205 J2	Q225 J2				
10	Q166 J2	Q186 J2	Q206 J2	Q226 J2				
	Q167 J2	Q187 J2	Q207 J2	Q227 J2				
	Q168 J2	Q188 J2	Q208 J2	Q228 J2				
	Q169 J2	Q189 J2	Q209 J2	Q229 J2				
	Q170 J2	Q190 J2	Q210 J2	Q230 J2				
15	Q171 J2	Q191 J2	Q211 J2	Q231 J2				
	Q172 J2	Q192 J2	Q212 J2	Q232 J2				
	Q173 J2	Q193 J2	Q213 J2	Q233 J2				
	Q174 J2	Q194 J2	Q214 J2	Q234 J2				
	Q175 J2	Q195 J2	Q215 J2	Q235 J2				
20	Q176 J2	Q196 J2	Q216 J2	Q236 J2				
	Q177 J2	Q197 J2	Q217 J2	Q237 J2				
	Q178 J2	Q198 J2	Q218 J2	Q238 J2				
	Q179 J2	Q199 J2	Q219 J2	Q239 J2				
	Q180 J2	Q200 J2	Q220 J2	Q240 J2				

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Table 14

	Z	W	Z	W	Z	W	Z	W
5	Q241 J2	Q261 J2	Q281 J2	Q301 J2				
	Q242 J2	Q262 J2	Q282 J2	Q302 J2				
	Q243 J2	Q263 J2	Q283 J2	Q303 J2				
	Q244 J2	Q264 J2	Q284 J2	Q304 J2				
	Q245 J2	Q265 J2	Q285 J2	Q305 J2				
10	Q246 J2	Q266 J2	Q286 J2	Q306 J2				
	Q247 J2	Q267 J2	Q287 J2	Q307 J2				
	Q248 J2	Q268 J2	Q288 J2	Q308 J2				
	Q249 J2	Q269 J2	Q289 J2	Q309 J2				
	Q250 J2	Q270 J2	Q290 J2	Q310 J2				
15	Q251 J2	Q271 J2	Q291 J2	Q311 J2				
	Q252 J2	Q272 J2	Q292 J2	Q312 J2				
	Q253 J2	Q273 J2	Q293 J2	Q313 J2				
	Q254 J2	Q274 J2	Q294 J2	Q314 J2				
	Q255 J2	Q275 J2	Q295 J2	Q315 J2				
20	Q256 J2	Q276 J2	Q296 J2	Q316 J2				
	Q257 J2	Q277 J2	Q297 J2	Q317 J2				
	Q258 J2	Q278 J2	Q298 J2					
	Q259 J2	Q279 J2	Q299 J2					
	Q260 J2	Q280 J2	Q300 J2					

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Table 15

	Z	W	Z	W	Z	W	Z	W
5	Q1	J4	Q21	J4	Q41	J4	Q61	J4
	Q2	J4	Q22	J4	Q42	J4	Q62	J4
	Q3	J4	Q23	J4	Q43	J4	Q63	J4
	Q4	J4	Q24	J4	Q44	J4	Q64	J4
	Q5	J4	Q25	J4	Q45	J4	Q65	J4
10	Q6	J4	Q26	J4	Q46	J4	Q66	J4
	Q7	J4	Q27	J4	Q47	J4	Q67	J4
	Q8	J4	Q28	J4	Q48	J4	Q68	J4
	Q9	J4	Q29	J4	Q49	J4	Q69	J4
	Q10	J4	Q30	J4	Q50	J4	Q70	J4
15	Q11	J4	Q31	J4	Q51	J4	Q71	J4
	Q12	J4	Q32	J4	Q52	J4	Q72	J4
	Q13	J4	Q33	J4	Q53	J4	Q73	J4
	Q14	J4	Q34	J4	Q54	J4	Q74	J4
	Q15	J4	Q35	J4	Q55	J4	Q75	J4
20	Q16	J4	Q36	J4	Q56	J4	Q76	J4
	Q17	J4	Q37	J4	Q57	J4	Q77	J4
	Q18	J4	Q38	J4	Q58	J4	Q78	J4
	Q19	J4	Q39	J4	Q59	J4	Q79	J4
	Q20	J4	Q40	J4	Q60	J4	Q80	J4

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Table 16

	Z	W	Z	W	Z	W	Z	W
5	Q81 J4	Q101 J4	Q121 J4	Q141 J4				
	Q82 J4	Q102 J4	Q122 J4	Q142 J4				
	Q83 J4	Q103 J4	Q123 J4	Q143 J4				
	Q84 J4	Q104 J4	Q124 J4	Q144 J4				
	Q85 J4	Q105 J4	Q125 J4	Q145 J4				
10	Q86 J4	Q106 J4	Q126 J4	Q146 J4				
	Q87 J4	Q107 J4	Q127 J4	Q147 J4				
	Q88 J4	Q108 J4	Q128 J4	Q148 J4				
	Q89 J4	Q109 J4	Q129 J4	Q149 J4				
	Q90 J4	Q110 J4	Q130 J4	Q150 J4				
15	Q91 J4	Q111 J4	Q131 J4	Q151 J4				
	Q92 J4	Q112 J4	Q132 J4	Q152 J4				
	Q93 J4	Q113 J4	Q133 J4	Q153 J4				
	Q94 J4	Q114 J4	Q134 J4	Q154 J4				
	Q95 J4	Q115 J4	Q135 J4	Q155 J4				
20	Q96 J4	Q116 J4	Q136 J4	Q156 J4				
	Q97 J4	Q117 J4	Q137 J4	Q157 J4				
	Q98 J4	Q118 J4	Q138 J4	Q158 J4				
	Q99 J4	Q119 J4	Q139 J4	Q159 J4				
	Q100 J4	Q120 J4	Q140 J4	Q160 J4				

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Table 17

	Z	W	Z	W	Z	W	Z	W
5	Q161 J4	Q181 J4	Q201 J4	Q221 J4				
	Q162 J4	Q182 J4	Q202 J4	Q222 J4				
	Q163 J4	Q183 J4	Q203 J4	Q223 J4				
	Q164 J4	Q184 J4	Q204 J4	Q224 J4				
	Q165 J4	Q185 J4	Q205 J4	Q225 J4				
10	Q166 J4	Q186 J4	Q206 J4	Q226 J4				
	Q167 J4	Q187 J4	Q207 J4	Q227 J4				
	Q168 J4	Q188 J4	Q208 J4	Q228 J4				
	Q169 J4	Q189 J4	Q209 J4	Q229 J4				
	Q170 J4	Q190 J4	Q210 J4	Q230 J4				
15	Q171 J4	Q191 J4	Q211 J4	Q231 J4				
	Q172 J4	Q192 J4	Q212 J4	Q232 J4				
	Q173 J4	Q193 J4	Q213 J4	Q233 J4				
	Q174 J4	Q194 J4	Q214 J4	Q234 J4				
	Q175 J4	Q195 J4	Q215 J4	Q235 J4				
20	Q176 J4	Q196 J4	Q216 J4	Q236 J4				
	Q177 J4	Q197 J4	Q217 J4	Q237 J4				
	Q178 J4	Q198 J4	Q218 J4	Q238 J4				
	Q179 J4	Q199 J4	Q219 J4	Q239 J4				
	Q180 J4	Q200 J4	Q220 J4	Q240 J4				

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Table 18

	Z	W	Z	W	Z	W	Z	W
5	Q241 J4	Q261 J4	Q281 J4	Q301 J4				
	Q242 J4	Q262 J4	Q282 J4	Q302 J4				
	Q243 J4	Q263 J4	Q283 J4	Q303 J4				
	Q244 J4	Q264 J4	Q284 J4	Q304 J4				
	Q245 J4	Q265 J4	Q285 J4	Q305 J4				
10	Q246 J4	Q266 J4	Q286 J4	Q306 J4				
	Q247 J4	Q267 J4	Q287 J4	Q307 J4				
	Q248 J4	Q268 J4	Q288 J4	Q308 J4				
	Q249 J4	Q269 J4	Q289 J4	Q309 J4				
	Q250 J4	Q270 J4	Q290 J4	Q310 J4				
15	Q251 J4	Q271 J4	Q291 J4	Q311 J4				
	Q252 J4	Q272 J4	Q292 J4	Q312 J4				
	Q253 J4	Q273 J4	Q293 J4	Q313 J4				
	Q254 J4	Q274 J4	Q294 J4	Q314 J4				
	Q255 J4	Q275 J4	Q295 J4	Q315 J4				
20	Q256 J4	Q276 J4	Q296 J4	Q316 J4				
	Q257 J4	Q277 J4	Q297 J4	Q317 J4				
	Q258 J4	Q278 J4	Q298 J4					
	Q259 J4	Q279 J4	Q299 J4					
	Q260 J4	Q280 J4	Q300 J4					

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Table 19

	Z	W	Z	W	Z	W	Z	W
5	Q1	J5	Q21	J5	Q41	J5	Q61	J5
	Q2	J5	Q22	J5	Q42	J5	Q62	J5
	Q3	J5	Q23	J5	Q43	J5	Q63	J5
	Q4	J5	Q24	J5	Q44	J5	Q64	J5
	Q5	J5	Q25	J5	Q45	J5	Q65	J5
10	Q6	J5	Q26	J5	Q46	J5	Q66	J5
	Q7	J5	Q27	J5	Q47	J5	Q67	J5
	Q8	J5	Q28	J5	Q48	J5	Q68	J5
	Q9	J5	Q29	J5	Q49	J5	Q69	J5
	Q10	J5	Q30	J5	Q50	J5	Q70	J5
15	Q11	J5	Q31	J5	Q51	J5	Q71	J5
	Q12	J5	Q32	J5	Q52	J5	Q72	J5
	Q13	J5	Q33	J5	Q53	J5	Q73	J5
	Q14	J5	Q34	J5	Q54	J5	Q74	J5
	Q15	J5	Q35	J5	Q55	J5	Q75	J5
20	Q16	J5	Q36	J5	Q56	J5	Q76	J5
	Q17	J5	Q37	J5	Q57	J5	Q77	J5
	Q18	J5	Q38	J5	Q58	J5	Q78	J5
	Q19	J5	Q39	J5	Q59	J5	Q79	J5
	Q20	J5	Q40	J5	Q60	J5	Q80	J5

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Table 20

	Z	W	Z	W	Z	W	Z	W
5	Q81 J5	Q101 J5	Q121 J5	Q141 J5				
	Q82 J5	Q102 J5	Q122 J5	Q142 J5				
	Q83 J5	Q103 J5	Q123 J5	Q143 J5				
	Q84 J5	Q104 J5	Q124 J5	Q144 J5				
	Q85 J5	Q105 J5	Q125 J5	Q145 J5				
10	Q86 J5	Q106 J5	Q126 J5	Q146 J5				
	Q87 J5	Q107 J5	Q127 J5	Q147 J5				
	Q88 J5	Q108 J5	Q128 J5	Q148 J5				
	Q89 J5	Q109 J5	Q129 J5	Q149 J5				
	Q90 J5	Q110 J5	Q130 J5	Q150 J5				
15	Q91 J5	Q111 J5	Q131 J5	Q151 J5				
	Q92 J5	Q112 J5	Q132 J5	Q152 J5				
	Q93 J5	Q113 J5	Q133 J5	Q153 J5				
	Q94 J5	Q114 J5	Q134 J5	Q154 J5				
	Q95 J5	Q115 J5	Q135 J5	Q155 J5				
20	Q96 J5	Q116 J5	Q136 J5	Q156 J5				
	Q97 J5	Q117 J5	Q137 J5	Q157 J5				
	Q98 J5	Q118 J5	Q138 J5	Q158 J5				
	Q99 J5	Q119 J5	Q139 J5	Q159 J5				
	Q100 J5	Q120 J5	Q140 J5	Q160 J5				

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Table 21

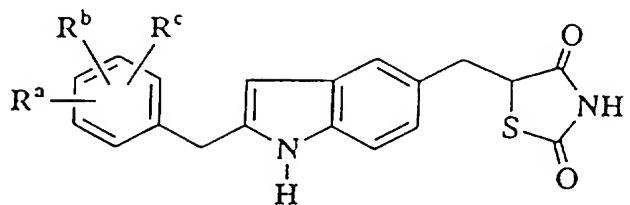
	Z	W	Z	W	Z	W	Z	W
5	Q161 J5	Q181 J5	Q201 J5	Q221 J5				
	Q162 J5	Q182 J5	Q202 J5	Q222 J5				
	Q163 J5	Q183 J5	Q203 J5	Q223 J5				
	Q164 J5	Q184 J5	Q204 J5	Q224 J5				
	Q165 J5	Q185 J5	Q205 J5	Q225 J5				
10	Q166 J5	Q186 J5	Q206 J5	Q226 J5				
	Q167 J5	Q187 J5	Q207 J5	Q227 J5				
	Q168 J5	Q188 J5	Q208 J5	Q228 J5				
	Q169 J5	Q189 J5	Q209 J5	Q229 J5				
	Q170 J5	Q190 J5	Q210 J5	Q230 J5				
15	Q171 J5	Q191 J5	Q211 J5	Q231 J5				
	Q172 J5	Q192 J5	Q212 J5	Q232 J5				
	Q173 J5	Q193 J5	Q213 J5	Q233 J5				
	Q174 J5	Q194 J5	Q214 J5	Q234 J5				
	Q175 J5	Q195 J5	Q215 J5	Q235 J5				
20	Q176 J5	Q196 J5	Q216 J5	Q236 J5				
	Q177 J5	Q197 J5	Q217 J5	Q237 J5				
	Q178 J5	Q198 J5	Q218 J5	Q238 J5				
	Q179 J5	Q199 J5	Q219 J5	Q239 J5				
	Q180 J5	Q200 J5	Q220 J5	Q240 J5				

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Table 22

	Z	W	Z	W	Z	W	Z	W
5	Q241 J5	Q261 J5	Q281 J5	Q301 J5				
	Q242 J5	Q262 J5	Q282 J5	Q302 J5				
	Q243 J5	Q263 J5	Q283 J5	Q303 J5				
	Q244 J5	Q264 J5	Q284 J5	Q304 J5				
	Q245 J5	Q265 J5	Q285 J5	Q305 J5				
10	Q246 J5	Q266 J5	Q286 J5	Q306 J5				
	Q247 J5	Q267 J5	Q287 J5	Q307 J5				
	Q248 J5	Q268 J5	Q288 J5	Q308 J5				
	Q249 J5	Q269 J5	Q289 J5	Q309 J5				
	Q250 J5	Q270 J5	Q290 J5	Q310 J5				
15	Q251 J5	Q271 J5	Q291 J5	Q311 J5				
	Q252 J5	Q272 J5	Q292 J5	Q312 J5				
	Q253 J5	Q273 J5	Q293 J5	Q313 J5				
	Q254 J5	Q274 J5	Q294 J5	Q314 J5				
	Q255 J5	Q275 J5	Q295 J5	Q315 J5				
20	Q256 J5	Q276 J5	Q296 J5	Q316 J5				
	Q257 J5	Q277 J5	Q297 J5	Q317 J5				
	Q258 J5	Q278 J5	Q298 J5					
	Q259 J5	Q279 J5	Q299 J5					
	Q260 J5	Q280 J5	Q300 J5					

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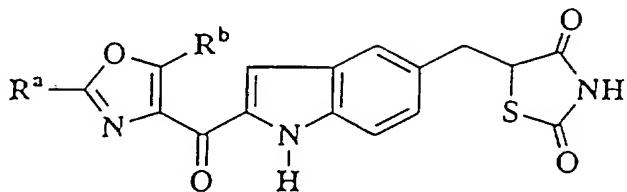


5

In the above formula,  $R^a$ ,  $R^b$  and  $R^c$  are selected from the following Table 23.

Table 23

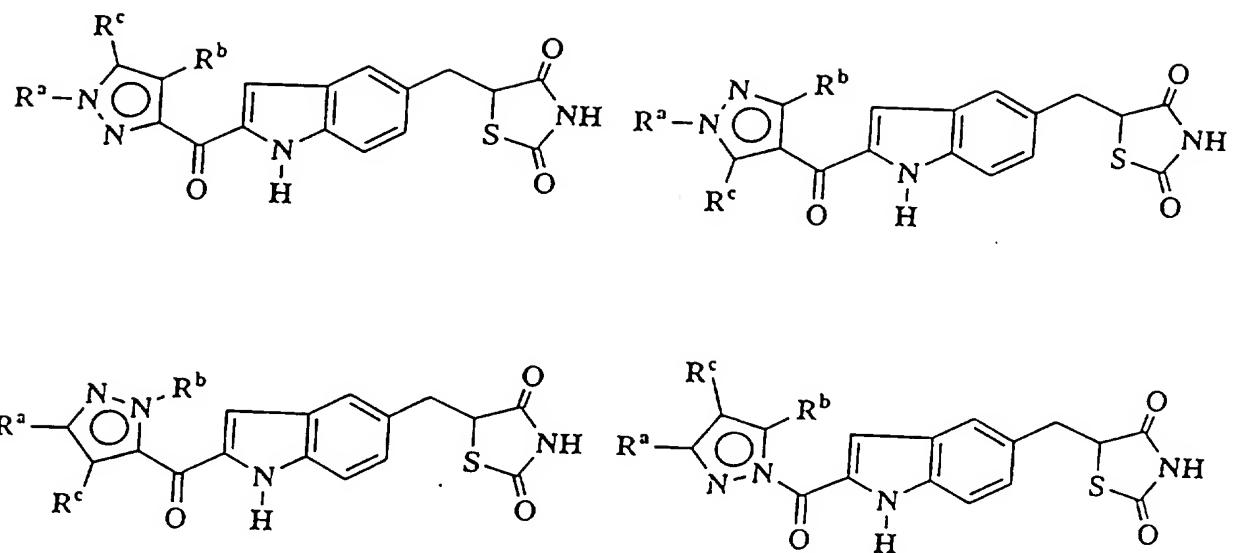
10	R <sup>a</sup>	R <sup>b</sup>	R <sup>c</sup>		R <sup>a</sup>	R <sup>b</sup>	R <sup>c</sup>
	2-Me	H	H		4-Q83	H	H
	3-Me	H	H		2-OH	H	H
	4-Me	H	H		3-OH	H	H
15	2-OMe	H	H		4-OH	H	H
	3-OMe	H	H		2-F	H	H
	4-OMe	H	H		3-F	H	H
	2-Ph	H	H		4-F	H	H
	3-Ph	H	H		2-Cl	H	H
20	4-Ph	H	H		3-Cl	H	H
	4-Q11	H	H		4-Cl	H	H
	4-Q18	H	H		2-Br	H	H
	4-Q19	H	H		3-Br	H	H
	4-Q49	H	H		4-Br	H	H
25	4-Q13	H	H		3-CF <sub>3</sub>	H	H
	4-OPh	H	H				



5 In the above formula, R<sup>a</sup>, R<sup>b</sup> and R<sup>c</sup> are selected from the following Table 24.

Table 24

	R <sup>a</sup>	R <sup>b</sup>	R <sup>a</sup>	R <sup>b</sup>	R <sup>a</sup>	R <sup>b</sup>
10	H	Me	Q6	Me	Q14	Me
	Me	Me	Q85	Me	Q49	Me
	Et	Me	Q86	Me	Q76	Me
	<sup>n</sup> Pr	Me	Q87	Me	Q13	Me
15	<sup>i</sup> Pr	Me	Q10	Me	OPh	Me
	<sup>t</sup> Bu	Me	Q88	Me	Q83	Me
	<sup>c</sup> Pr	Me	Q89	Me	Ph	H
	<sup>c</sup> Hex	Me	Q8	Me	Ph	Me
	Q84	Me	Q90	Me	Ph	Et
20	Ph	Me	Q91	Me	Ph	<sup>n</sup> Pr
	Q1	Me	4-Ph-Ph	Me	Ph	<sup>i</sup> Pr
	Q2	Me	Q11	Me	Ph	<sup>t</sup> Bu
	Q3	Me	Q12	Me	Ph	<sup>c</sup> Pr
	Q4	Me	Q18	Me	Ph	<sup>c</sup> Hex
25	Q5	Me	Q19	Me	Ph	Ph



In the above formula, R<sup>a</sup>, R<sup>b</sup> and R<sup>c</sup> are selected from the following Table 25.

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Table 25

	R <sup>a</sup>	R <sup>b</sup>	R <sup>c</sup>	R <sup>a</sup>	R <sup>b</sup>	R <sup>c</sup>
5	H	Me	H	Q90	Me	H
	Me	Me	H	Q91	Me	H
	Et	Me	H	4-Ph-Ph	Me	H
	<sup>n</sup> Pr	Me	H	Q11	Me	H
	<sup>i</sup> Pr	Me	H	Q12	Me	H
	<sup>t</sup> Bu	Me	H	Q18	Me	H
10	<sup>c</sup> Pr	Me	H	Q19	Me	H
	<sup>c</sup> Hex	Me	H	Q14	Me	H
	Q84	Me	H	Q49	Me	H
	Ph	Me	H	Q76	Me	H
	Q1	Me	H	Q13	Me	H
	Q2	Me	H	OPh	Me	H
15	Q3	Me	H	Q83	Me	H
	Q4	Me	H	Ph	H	H
	Q5	Me	H	Ph	Me	H
	Q6	Me	H	Ph	Et	H
	Q85	Me	H	Ph	<sup>n</sup> Pr	H
	Q86	Me	H	Ph	<sup>i</sup> Pr	H
20	Q87	Me	H	Ph	<sup>t</sup> Bu	H
	Q10	Me	H	Ph	<sup>c</sup> Pr	H
	Q88	Me	H	Ph	<sup>c</sup> Hex	H
	Q89	Me	H	Ph	Ph	H
	Q8	Me	H	Ph	Me	Me

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As evident from the following test results, the compound (I) or its pharmaceutically acceptable salt of the present invention has a hypoglycemic activity, and can be used alone or in a mixture with a known

5 pharmaceutically acceptable binder, excipient, lubricant or disintegrator, for preventing or treating diabetes mellitus of mammals including humans, mice, rats, rabbits, dogs, monkeys, cows, horses, pigs and the like.

10 The compound (I) or its pharmaceutically acceptable salt of the present invention can also be used for preventing or treating diabetic complications including diabetic eye diseases (such as diabetic cataract and diabetic retinopathy), diabetic neuropathy, diabetic nephropathy, diabetic gangrene, and the like. The compound (I) or its 15 pharmaceutically acceptable salt of the present invention can also be used in combination with various oral hypoglycemic agents such as insulin derivatives, sulfonylurea derivatives and biguanide derivatives, and aldose-reductase inhibitory agents.

20 The compounds (I) of the present invention may be formulated into various suitable formulations depending upon the manner of administration. The compounds of the present invention may be administered in the form of free thiazolidindione or in the form of physiologically 25 hydrolyzable and acceptable pharmaceutically acceptable salts (such as sodium salts or potassium salts).

The pharmaceutical composition of the present

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invention is preferably administered orally in the form of the compound of the present invention by itself or in the form of powders, granules, tablets or capsules formulated by mixing the compound of the present

5 invention with a suitable pharmaceutically acceptable carrier including a binder (such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone or CMC-Ca), an excipient (such as lactose, sugar, corn starch, calcium

10 phosphate, sorbitol, glycine or microcrystal cellulose powder), a lubricant (such as magnesium stearate, talc, polyethylene glycol or silica), and a disintegrator (such as potato starch).

However, the pharmaceutical composition of the

15 present invention is not limited to such oral administration and it is applicable for parenteral administration. For example, it may be administered in the form of e.g. a suppository formulated by using oily base material such as cacao butter, polyethylene glycol,

20 lanolin or fatty acid triglyceride, a transdermal therapeutic base formulated by using liquid paraffin, white vaseline, a higher alcohol, Macrogol ointment, hydrophilic ointment or hydro-gel base material, an injection formulation formulated by using one or more

25 materials selected from the group consisting of polyethylene glycol, hydro-gel base material, distilled water, distilled water for injection and an excipient

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such as lactose or corn starch, or a formulation for administration through mucous membranes such as an ocular mucous membrane, a nasal mucous membrane and an oral mucous membrane.

5        The daily dose of the compound of the present invention is from 0.05 to 50 mg, preferably from 0.1 to 10 mg per kg weight of a patient, and it is administered from once to three times per day. The dose may of course be varied depending upon the age, the weight or the  
10      condition of illness of a patient.

#### EXAMPLES

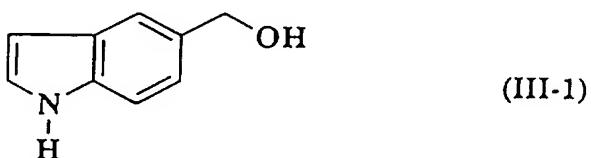
Now, the present invention will be described in further detail with reference to Examples for preparation of the compounds of the present invention,  
15      Pharmacological Test Examples and Formulation Examples. However, it should be understood that the present invention is by no means restricted by such specific Examples.

Reference 1 Synthesis of hydroxymethylindole (Compound  
20      (III))

#### Synthesis Route 1

#### Synthesis of 5-hydroxymethylindole (III-1)

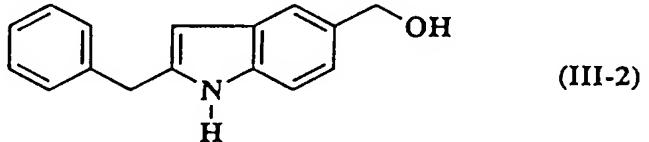
25



10.60 g ( 65.77 mmol) of 5-indolecarboxylic acid was

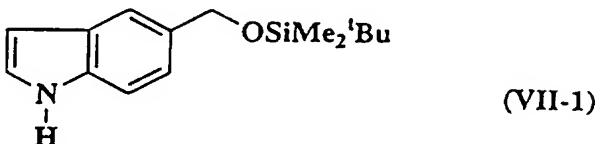
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dissolved in 120 ml of tetrahydrofuran, and was cooled to 0°C. To the resultant mixture, 9.98 g (263.09 mmol) of lithium aluminum hydride was added little by little. After gradually rising reaction temperature to room 5 temperature, a resultant mixture was heated under reflux for 30 minutes. To the resultant reaction mixture, were added little by little Celite, ethyl acetate, methanol and water in this order, and the mixture was quenched with an excess amount of a reducing agent. A resultant 10 reaction mixture was filtrated by means of a small amount of silica gel. The solvent in the filtrate was removed by distillation under reduced pressure to obtain a 9.50 g (98.1%) of the subject compound (III-1).  
Colorless plate-like crystals  
15 Melting point: 58-58.5°C (solvent for recrystallization: diethylether/hexane)  
60MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$ : 2.10(1H, brs), 4.60(2H, s), 6.35(1H, dd,  $J=4.0, 3.0\text{Hz}$ ), 6.80-7.30(3H, m), 7.41(1H, brs), 8.22(1H, brs).  
MS(EI) m/e: 147( $\text{M}^+$ ), 130, 118.  
20 Synthesis route 2  
Synthesis of 2-benzyl-5-hydroxymethylindole (III-2)



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## 5-t-butyldimethylsilyloxyethylindole (Compound (VII-1))



5

9.50 g (65.55 mmol) of Compound (III-1) was dissolved in 40 ml of dimethylformamide dehydrated with molecular sieves, and 6.96 g (98.325 mmol) of imidazole and 11.85 g (78.66 mmol) of t-butyldimethylsilyl chloride were added thereto and were stirred at room temperature for 10 hours. After finishing the reaction, a saturated sodium chloride aqueous solution was added to the reaction solution, and the mixture was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The washed organic phase was then dried with anhydrous sodium sulfate, and the residue obtained after removing a solvent by distillation under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane=1/4). The product thus obtained was further recrystallized to obtain 13.05 g of the subject compound (VII-1).

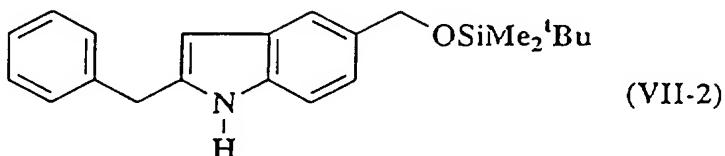
Colorless plate-like crystals

Melting point: 48-49°C (solvent used for  
 25 recrystallization: diethylether/hexane)  
 60MHz <sup>1</sup>H-NMR(CDCl<sub>3</sub>),  $\delta$ : 0.10(6H, s), 0.92(9H, s), 4.75(2H, s), 6.40(1H, d, J=4.0, 3.0Hz), 6.92-7.35(3H, m), 7.45(1H, brs), 8.00(1H, brs).  
 MS(EI) m/e: 261(M<sup>+</sup>), 246, 204, 130.

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2-benzyl-5-t-butyldimethylsilyloxymethylindole (Compound (VII-2))

5



To an anhydrous tetrahydrofuran (5 ml) solution of 555.5 mg (2.1248 mmol) of Compound (VII-1), was dropwise added 1.3 ml (2.1248 mmol) of butyl lithium (1.6 M hexane solution) at -78°C, and the resultant mixture was stirred for 15 minutes. Dry carbon dioxide gas was passed through the reaction solution for 15 minutes. After fully removing carbon dioxide gas at a reaction temperature of 20°C, the reaction temperature was lowered to -78°C. After fully cooling, 2.8 ml (4.2496 mmol) of t-butyl lithium (1.54 M solution in pentane) was dropwise added thereto, and the resultant mixture was stirred for 2 hours. Thereafter, an anhydrous tetrahydrofuran (2 ml) solution of 726.9 mg (4.2496 mmol) of benzylbromide (Compound (VIII-1)) was added thereto at room temperature. After stirring the reaction mixture at -78°C for 30 minutes, the reaction mixture was further stirred at room temperature for 30 minutes and further stirred at a refluxing temperature of a solvent for 15 minutes. After terminating the reaction by adding methylene chloride and 2M hydrochloric acid to the reaction solution, an organic phase obtained was washed

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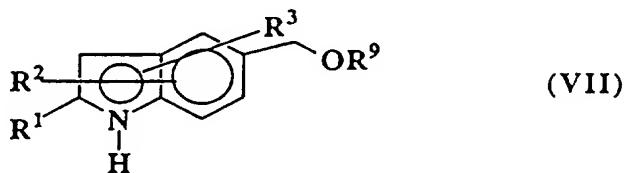
with a saturated ammonium chloride aqueous solution. After drying the organic phase thus obtained with anhydrous sodium sulfate, a residue obtained after removing a solvent by distillation under reduced pressure 5 was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/4) and was repeatedly subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/15) to obtain 111.9 mg (15.0%) of the subject compound (VII-2).

10 Yellow oily material

60MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$  :0.10(6H, s), 0.92(9H, s), 4.00(2H, s), 4.72(2H, s), 6.18(1H, d,  $J=2.0\text{Hz}$ ), 6.90-7.30(2H, m), 7.38(1H, brs), 7.51(1H, brs).MS (EI)  $m/e$ :351( $\text{M}^+$ ), 294, 235, 220, 149.

15 In the same manner as above, electrophilic reagents (Compound (VIII)) were used to Compound (VII-1) in place of benzylbromide to synthesize the following compounds ( $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  in the table correspond to the substituents of Compound (VII)).

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5 (R<sup>n</sup>=H, R<sup>1</sup>=W-Z, R<sup>9</sup>=SiMe<sub>2</sub>Bu<sup>t</sup>)

	Compound No.	R <sup>1</sup>	R <sup>2</sup> R <sup>3</sup>	Electrophile (VIII)	Properties (mp °C)
10	VII-3		H H		Colorless needles (104-105)
15	VII-4		H H		Yellow crystals (135-138)

15 Compound (VII-3)

60MHz <sup>1</sup>H-NMR(CDCl<sub>3</sub>), δ: 0.90(6H, s), 0.92(9H, s), 2.27(3H, s), 3.96(2H, s), 4.75(2H, s), 6.21(1H, d, J=2.0Hz), 6.90-7.70(6H, m), 7.75-8.15(2H, m), 8.77(1H, brs).

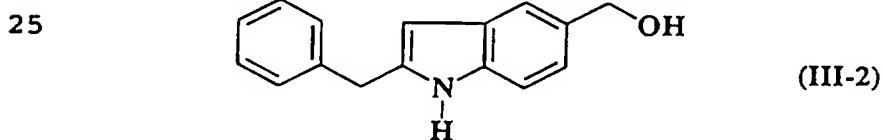
MS(EI) m/e:432(M<sup>+</sup>), 417, 375, 301, 156, 105, 75.

20 Compound (VII-4)

60MHz <sup>1</sup>H-NMR(CDCl<sub>3</sub>), δ: 1.12(6H, s), 1.95(9H, s), 2.68(3H, s), 4.75(2H, s), 7.00-8.30(9H, m), 9.32(1H, brs).

MS(FD) m/e:446.

2-benzyl-5-hydroxymethylindole (Compound (III-2))



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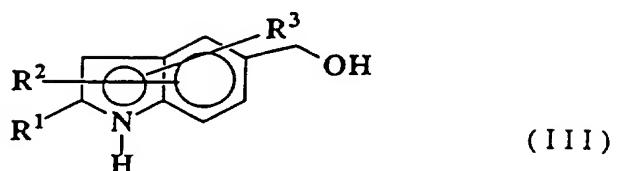
To a tetrahydrofuran (5 ml) solution of 111.9 mg (0.3183 mmol) of Compound (VII-2), was added a tetrahydrofuran (1 ml) solution of 166.4 mg (2.041 mmol) of tetra-n-butylammonium fluoride. After stirring the 5 resultant mixture at room temperature for 3 hours, 166.4 mg (2.041 mmol) of tetra-n-butyl ammonium fluoride was further added thereto and was stirred at room temperature for 2 hours. The resultant reaction solution was extracted by adding 2M-hydrochloric acid, water and 10 chloroform. An organic phase obtained was dried with anhydrous sodium sulfate, and a residue obtained after removing a solvent under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain 57.7 mg (76.4%) of the 15 subject compound (III-2).

Yellow crystals

60MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$ : 1.75(1H, s), 4.00(2H, s), 4.62(1H, s), 6.20(1H, d,  $J=2.0\text{Hz}$ ), 7.00-7.35(2H, m), 7.39(1H, brs), 7.83(1H, brs).

In the same manner as above, Compound (VII-3 and VII-20 4) were used to synthesize the following compounds ( $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  in the Table correspond to the substituents of Compound (III)).

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5

(R<sup>n</sup>=H, R<sup>1</sup>=W-Z)

	Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Properties (mp °C)
10	III-3		H	H	Pale yellow needles (104-105)
	III-4		H	H	Pale yellow needles (225-226)

**Compound (III-3)**

60MHz <sup>1</sup>H-NMR(CDCl<sub>3</sub>), δ : 2.09(1H, brs), 2.22(3H, s), 3.89(2H, s), 4.62(2H, s), 6.18(1H, brs), 6.80-7.60(6H, m), 7.70-8.10(2H, m), 8.92(1H, brs).  
 15 MS(EI) m/e:318(M<sup>+</sup>), 301, 287, 275, 172, 147, 130, 115, 105, 77.

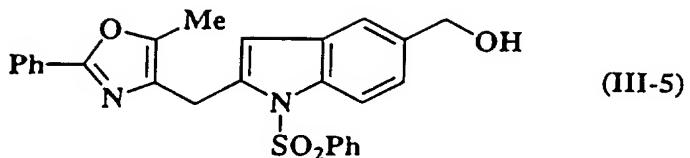
**Compound (III-4)**

500MHz <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>), δ : 2.65(3H, s), 4.58(2H, d, J=5.6Hz), 5.15(1H, t, J=5.6Hz), 7.31(1H, dd, J=8.5, 1.0Hz), 7.48(1H, d, J=8.5Hz), 7.53(1H, t, J=7.3Hz), 7.66(2H, t, J=7.3Hz), 7.73(1H, s), 7.96(1H, d, J=1.0Hz), 8.20(2H, d, J=7.3Hz), 11.92(1H, brs).  
 20 MS(EI) m/e:332(M<sup>+</sup>), 315, 301, 285, 186, 174, 156, 144, 128, 117, 91, 77.

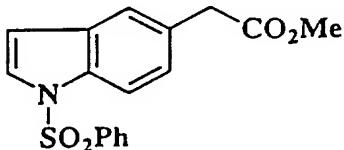
**Synthesis Route 3**

25 **Synthesis of 1-benzenesulfonyl-5-hydroxymethyl-2-(2-phenyl-5-methyloxazole-4-yl) methylindole (Compound III-5)**

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## 5 Methyl 5-(1-benzenesulfonyl)indolecarboxylate



10 1.0470 g (6.4966 mmol) of 5-indolecarboxylic acid was dissolved in 10 ml of acetone and was reacted with an excess amount of diazomethane at room temperature. After finishing the reaction, a residue obtained by removing a solvent under reduced pressure was subjected to silica 15 column chromatography (eluent: ethyl acetate/hexane = 1/2) to obtain 1.1123 g (97.7%) of methyl 5-indolecarboxylate.

Colorless crystals

60MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$ : 3.78(3H, s), 6.52(1H, dd,  $J=3.0, 3.0\text{Hz}$ ), 7.12(1H, d,  $J=3.0\text{Hz}$ ), 7.28(1H, d,  $J=9.0\text{Hz}$ ), 7.82(1H, dd,  $J=9.0, 2.0\text{Hz}$ ), 8.30(1H, d,  $J=2.0\text{Hz}$ ), 8.51(1H, brs).

MS(EI)  $m/e: 175(\text{M})^+$ , 149, 144, 116.

67.8 mg (2.8262 mmol) of sodium hydride was suspended in 2 ml of dimethylformamide dehydrated with molecular 25 sieves. To the suspension thus obtained, was added a molecular sieves-dehydrated dimethylformaldehyde (5 ml) solution of 412.6 mg (2.3552 mmol) of methyl 5-

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indolecarboxylate at room temperature. After stirring the resultant mixture for 40 minutes, a molecular sieves-dehydrated dimethylformaldehyde (2 ml) solution of 832.0 mg (4.7104 mmol) of benzenesulfonyl chloride was added 5 thereto at room temperature and was stirred for 2 hours. Water was added to the reaction solution and the reaction solution was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The washed organic 10 phase was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was washed with hexane to obtain 729.9 mg (98.3%) of the aimed methyl 5-(1-benzenesulfonyl)indolecarboxylate.

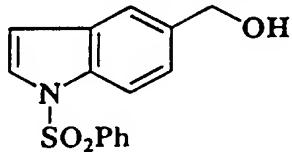
15 Colorless crystals

Melting point: 149-149.5°C (solvent used for recrystallization: benzene)

60MHz  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ),  $\delta$  :3.90(3H, s), 6.67(1H, d,  $J=5.0\text{Hz}$ ), 7.20-8.40(9H, m).

20 MS(EI)  $m/e$ :315( $\text{M}^+$ ), 284, 174, 159, 143, 115.

1-benzenesulfonyl-5-hydroxymethylindole



25 508.7 mg (1.6131 mmol) of methyl 5-(1-benzenesulfonyl)indolecarboxylate was dissolved in 5 ml of tetrahydrofuran dehydrated with molecular sieves and

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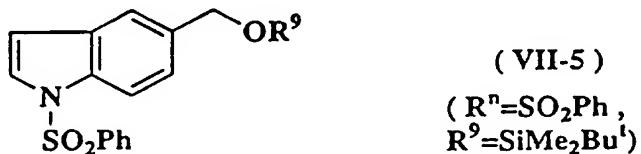
6.32 ml (3.2263 mmol) of diisobutylaluminium hydride (1.02 M toluene solution) was gradually dropwise added thereto at room temperature and the resultant mixture was stirred at room temperature for 30 minutes. To the 5 resultant reaction solution, were added Celite, water and ethylacetate in this order, and the resultant reaction solution was filtrated by a filter paper and the filtrate was washed with a saturated sodium chloride aqueous solution. An organic phase obtained was dried with 10 anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was then filtrated by silica gel to obtain 508.8 mg of aimed material. The compound thus obtained was used in the following reaction without further purifying.

15 Colorless oily material

60MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$ :4.65(2H, brs), 6.55(1H, d,  $J=5.0\text{Hz}$ ), 7.00-8.10(9H, m).

MS(EI)  $m/e$ :287( $\text{M}^+$ ), 270, 141, 129, 118, 91, 77.

1-benzenesulfonyl-5-t-butyldimethylsilyloxymethylinole  
20 (Compound (VII-5))



25 508.8 mg (1.6131 mmol) of 1-benzenesulfonyl-5-hydroxymethylinole was dissolved in 5 ml of dimethylformamide dehydrated with molecular sieves, and

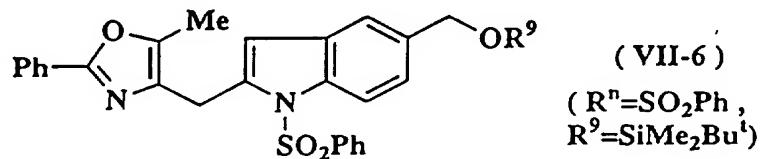
- 183 -

164.7 mg (2.4197 mmol) of imidazole and 486.2 mg (3.2262 mmol) of t-butyldimethylsilyl chloride were added thereto and the resultant mixture was stirred at room temperature for 16 hours. After finishing the reaction, the 5 saturated sodium chloride aqueous solution was added to the resultant reaction solution and the resultant reaction solution was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The organic 10 phase thus obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/4) to obtain 611.9 mg (94.5%) of the subject compound 15 (VII-5)

Colorless oily material

60MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$ : 0.07(6H, s), 0.90(9H, s), 4.70(2H, s), 7.00-8.00 (9H, m).

1-benzenesulfonyl-2-(2-phenyl-5-methyloxazole-4-  
20 yl)methyl-5-t-butyldimethylsilyloxymethyldiindole (Compound  
(VII-6))



25

To an anhydrous tetrahydrofuran (2 ml) solution of 167.1 mg (0.4161 mmol) of Compound (VII-5), was dropwise

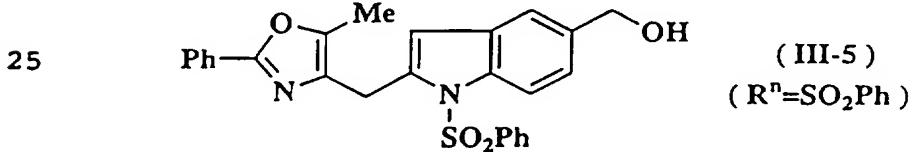
- 184 -

added 0.35 ml (0.5409 mmol) of t-butyllithium (1.54 M solution in pentane) at -12°C. After rising the reaction temperature to room temperature, the reaction mixture was stirred for 30 minutes, and 248.9 mg (0.8322 mmol) of 2-5 phenyl-5-methyloxazole-4-ylmethyl iodide (Compound (VIII-2)) and anhydrous tetrahydrofuran (2 ml) solution were added thereto at room temperature. After stirring the mixture for 1 hour, water was added to the reaction solution and the reaction solution was extracted with 10 ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The organic phase thus obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was subjected to a silica 15 gel column chromatography (eluent: ethyl acetate/hexane = 1/7) repeatedly to obtain 160.9 mg (67.5%) of the subject compound (VII-6).

Light-yellow oily material

60MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$ : 0.12(6H, s), 0.90(9H, s), 2.22(3H, s), 4.22(2H, s), 16 4.72(2H, s), 6.27(1H, s), 6.80-8.20(13H, m).  
20 MS(EI)  $m/e$ : 572( $\text{M}^+$ ), 515, 441, 374, 299, 105.

1-benzenesulfonyl-2-(2-phenyl-5-methyloxazole-4-yl)methyl-5-hydroxymethylindole (Compound (III-5))



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To a tetrahydrofuran (1 ml) solution of 46.9 mg (0.0819 mmol) of Compound (VII-6), was added 0.5 ml of tetra-n-butylammonium fluoride (1M THF solution). After stirring the resultant mixture for 1 hour at room 5 temperature, the water was added to the resultant reaction solution and the reaction solution was extracted with chloroform. An organic phase obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was subjected 10 to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/2) to obtain quantitatively 39.5 mg of the subject compound (III-5).

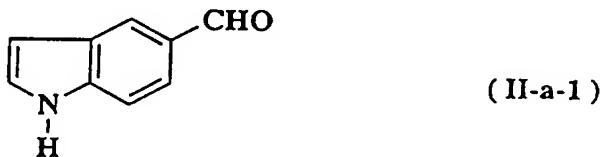
Light-yellow oily material

60MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$  :3.22(3H, s), 4.22(2H, s), 4.66(2H, s), 6.28(1H, s),  
15 6.80-8.30(13H, m).  
MS(EI) m/e:458( $\text{M}^+$ ), 317, 300, 287, 245, 217, 195, 154, 105, 77.

Reference Example 2 Synthesis of formylindole (Compound II)

20 Synthesis Route 1

Synthesis of 5-formylindole (II-a-1)



25

750.2 mg (5.0971 mmol) of 5-hydroxymethylindole (Compound (III-1)) was dissolved in 14 ml of

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tetrahydrofuran, and 4.4314 g (50.971 mmol) of activated manganese dioxide was added thereto and the resultant mixture was heat-refluxed for 17 hours. After the reaction mixture was filtrated to remove an oxidizing agent residue, yellow brown crystals (657.0 mg) obtained were subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain 602.6 mg (81.4%) of the subject compound (II-a-1)

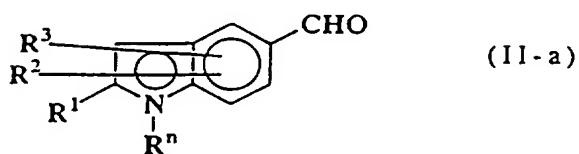
Light yellow crystals Melting point: 95-96°C

10 60MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 6.50(1H, dd, J=3.0, 2.0Hz), 7.18(1H, d, J=3.0Hz), 7.36(1H, d, J=9.0Hz), 7.68(1H, dd, J=9.0, 1.0Hz), 8.05(1H, brs), 8.75(1H, brs), 9.90(1H s).

MS(EI) m/e:145(M)<sup>+</sup>, 116, 89.

15 In the same manner as above, the following compounds were synthesized (R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>n</sup> in the table correspond to the substituents of Compound (II)).

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	Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting material (III)	Properties (mp °C)
5	II-a-2	2-	H	H	H	III-2	Yellow crystals (108-109)
10	II-a-3	2-	H	H	H	III-3	Pale yellow crystals (127-128)
15	II-a-4	2-	H	H	H	III-4	Pale yellow powder (258.5-259.5)
	II-a-5	2-	H	H	SO <sub>2</sub> Ph	III-5	Yellow amorphous

15

## Compound (II-a-2)

60MHz <sup>1</sup>H-NMR(CDCl<sub>3</sub>), δ: 4.08(2H, s), 6.36(1H, brs), 6.88-7.50(6H, m), 7.58(1H, dd, J=9.0, 2.0Hz), 7.97(1H, brs), 8.30(1H, brs), 9.85(1H, s).  
 MS(EI) m/e: 235(M<sup>+</sup>), 206, 158, 129, 115, 102, 91, 77.

20 Compound (II-a-3)

60MHz <sup>1</sup>H-NMR(CDCl<sub>3</sub>), δ: 2.27(3H, s), 3.92(2H, s), 6.35(1H, brs), 7.10-8.05(8H, m), 9.55(1H, brs), 9.81(1H, s).  
 MS(EI) m/e: 316(M<sup>+</sup>), 287, 273, 170, 115, 105, 77.

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**Compound (II-a-4)**

500MHz  $^1\text{H-NMR}$  (DMSO-d<sub>6</sub>),  $\delta$  : 2.67(3H, s), 7.54(1H, t,  $J=7.3\text{Hz}$ ), 7.66(1H, d,  $J=9.8\text{Hz}$ ), 7.70(2H, t,  $J=7.8\text{Hz}$ ), 7.84(1H, dd,  $J=9.8, 1.0\text{Hz}$ ), 8.21(2H, d,  $J=7.8\text{Hz}$ ), 8.24(1H, s), 8.49(1H, d,  $J=1.0\text{Hz}$ ), 10.02(1H, s, -CHO), 12.47(1H, brs).

5 MS(EI) m/e:330(M $^+$ ), 301, 172, 117, 91, 77.

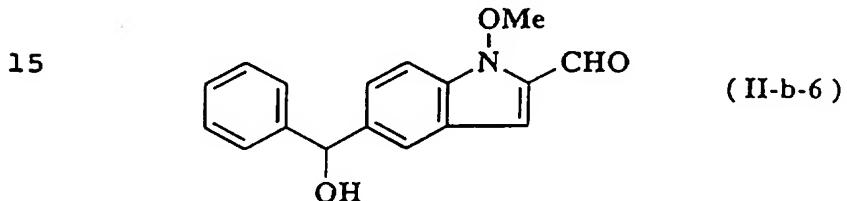
**Compound (II-a-5)**

60MHz  $^1\text{H-NMR}$  (CDCl<sub>3</sub>),  $\delta$  : 2.27(3H, s), 4.26(2H, s), 6.42(1H, s), 7.10-8.40(13H, m), 9.92(1H, s).

10 MS(EI) m/e:456(M $^+$ ), 315, 105, 77.

**Synthesis Route 2**

**Synthesis of 2-formyl-5-(1-hydroxybenzyl)-1-methoxyindole (Compound (II-a-6))**



20 2-formylindole (Compound (II-b)) can be obtained by conducting formylation at the 2-position of 5-bromo-1-methoxyindole synthesized through 5-boromoindoline using 5-bromoindole as a starting material.

25 1.09 g (5.5598 mmol) of 5-bromoindole was dissolved in 20 ml of acetic acid, and 2.1 g (33.3 mmol) of sodium cyanoborohydride was added little by little thereto at room temperature. After stirring the resultant mixture at room temperature for 20 minutes, acetic acid was

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removed by distillation. 40% sodium hydroxide was then added thereto, and the resultant reaction solution was completely neutralized with acetic acid and was extracted with ethyl acetate. After an organic phase obtained was 5 dried with anhydrous sodium sulfate, a residue obtained by removing a solvent by distillation under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 2/1) to obtain 904.2 mg (82.1%) of 5-boromoindoline.

10 Colorless oily material

60MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$  : 2.90(2H, brt,  $J=8.0\text{Hz}$ ), 3.42(2H, brt,  $J=8.0\text{Hz}$ ), 3.42(1H, brs), 6.30(1H, d,  $J=9.0\text{Hz}$ ), 6.95(1H, dd,  $J=9.0$ , 2.0Hz), 7.01(1H, d,  $J=2.0\text{Hz}$ ).

MS(EI) m/e:199( $\text{M}^+$ ), 197( $\text{M}^+$ ), 117, 89.

15 5-bromo-1-methoxyindole (Compound (IX-1))



20 904.2 mg (4.565 mmol) of 5-boromoindoline was converted by the method disclosed in "Heterocycles" by M. Somei and T. Kawasaki, 1989, 29, 1251 to 739.3 mg (3.2701 mmol, 71.6%) of the subject compound (IX)-1).

Colorless column-like crystals

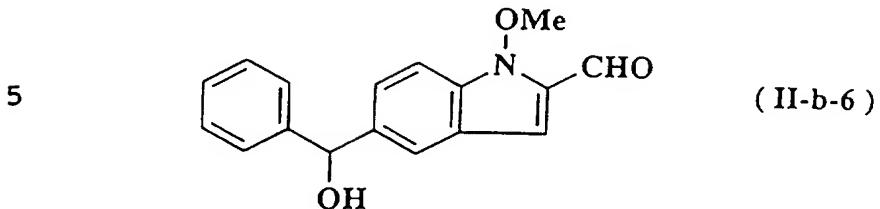
25 Melting point: 44-45°C

500MHz  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ),  $\delta$  : 4.08(3H, s), 6.29(1H, d,  $J=3.4\text{Hz}$ ), 7.25(1H, d,  $J=3.4\text{Hz}$ ), 7.31(1H, brs), 7.71(1H, brs).

MS(EI) m/e:227( $\text{M}^+$ ), 225( $\text{M}^+$ ), 212, 210, 196, 194, 115, 88.

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2-formyl-5-(1-hydroxybenzyl)-1-methoxyindole (Compound (II-b-6))



To an anhydrous tetrahydrofuran (5 ml) solution of 492.9 mg (2.1802 mmol) of Compound (IX-1), was dropwise 10 added 2.35 ml of phenyl lithium (1.02 M solution in ether-cyclohexane, 2.3982 mmol) at -16°C under argon atmosphere. After 15 minutes, 159.4 mg (2.1802 mmol) of anhydrous dimethylformamide was added thereto. After the resultant mixture was stirred at -16°C for 15 minutes as 15 it was, the reaction temperature was lowered to -78°C. After fully lowering the reaction temperature, 2.02 ml of t-butyl lithium (1.61 M solution in pentane, 3.2703mmol) was dropwise added thereto. After 10 minutes, 0.66 ml (6.5406 mmol) of benzaldehyde (Compound (VIII-4)) was 20 added thereto, and the resultant mixture was stirred for 10 minutes. 20 ml of water was added to the resultant reaction mixture, and the reaction mixture was extracted with ethyl acetate to obtain an organic phase. The organic phase thus obtained was washed with a saturated 25 sodium chloride aqueous solution, and the washed organic phase was dried with anhydrous sodium sulfate. Thereafter, the residue obtained by removing a solvent by

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distillation under reduced pressure was subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/3) to obtain 494.7 mg (80.7%) of the subject compound (II-b-6).

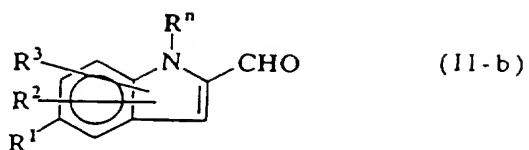
5 Light-yellow oily material

500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 2.32(1H, brs), 4.15(3H, s), 5.95(1H, s), 7.09(1H, d, J=0.7Hz), 7.28(1H, brt, J=8.0Hz), 7.35(2H, brt, J=8.0Hz), 7.41(2H, brd, J=8.0Hz), 7.43(1H, dd, J=9.0, 1.5Hz), 7.46(1H, ddd, J=9.0, 1.5, 0.7Hz), 7.73(1H, dd, J=1.5, 0.7Hz), 9.90(1H, s).

10 MS(EI) m/e: 281(M<sup>+</sup>), 264, 176, 148, 117, 105, 77.

In the same manner as above, electrophilic reagents (Compound (VIII)) were used in place of benzaldehyde to synthesize the following compounds (R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and Z in the table correspond to the substituent of Compound (II-b)).

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Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Electrophile (VIII)	Properties (mp °C)
II-b-7		H	H	MeO		Yellow oil
II-b-8		H	H	MeO		Pale yellow plates (168-168.5)
II-b-9		H	H	MeO		Colorless needles (176.5-177.5, decomp.)
II-b-10		H	H	MeO		Pale yellow plates (147-148)
II-b-11		H	H	MeO		Yellow oil
II-b-12		H	H	MeO		Yellow oil

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Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Electrophile (VIII)	Properties (mp °C)
II-b-13		H	H	MeO		Yellow oil
II-b-14		H	H	MeO		Yellow oil
II-b-15		H	H	MeO		Yellow oil
II-b-16		H	H	MeO		Yellow oil
II-b-17		H	H	MeO		Pale yellow needles (162.5-163.5)

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**Compound (II-b-7)**

500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 2.39(1H, brs), 4.15(3H, s), 6.12(1H, brs), 7.09  
 (1H, s), 7.40-7.52(4H, m), 7.72-7.80(3H, m), 7.94(1H, brs), 9.91(1H, s).  
 MS(EI) m/e: 331(M<sup>+</sup>), 314, 299, 283, 270, 254, 241, 226, 215, 202, 172, 1  
 5 55, 127, 116, 101, 89.

**Compound (II-b-8)**

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 4.09(3H, s), 6.10(1H, d, J=3.9Hz), 6.29(1H, d,  
 J=3.9Hz), 7.35(1H, s), 7.51(1H, d, J=8.0Hz), 7.55(1H, d, J=8.0Hz), 7.59  
 (1H, dd, J=8.0, 8.0Hz), 7.71(1H, dd, J=8.0, 8.0Hz), 7.89(1H, s), 7.98(1H,  
 10 d, J=9.0Hz), 7.99(1H, d, J=9.0Hz), 8.33(1H, brs), 8.90(1H, d, J=1.0Hz),  
 9.91(1H, s).  
 MS(EI) m/e: 332(M<sup>+</sup>), 315, 255, 245, 202, 156, 128, 117.

**Compound (II-b-9)**

500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 2.72(3H, s), 4.24(3H, s), 7.32(1H, s), 7.41(1H,  
 15 brt, J=7.6Hz), 7.52(2H, brt, J=7.6Hz), 7.63(1H, dd, J=8.8, 0.7Hz), 8.12  
 (2H, brd, J=7.6Hz), 8.39(1H, dd, J=8.8, 1.5Hz), 8.86(1H, dd, J=1.5, 0.7Hz),  
 9.98(1H, s).  
 MS(EI) m/e: 360(M<sup>+</sup>), 329, 310, 202, 186, 172, 143, 115, 91, 77.

**Compound (II-b-10)**

20 500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 2.86(1H, brs), 4.17(3H, s), 7.04(1H, s), 7.26-7.  
 37(10H, m), 7.45-7.48(2H, m), 7.50-7.52(1H, m), 9.89(1H, s).  
 MS(EI) m/e: 357(M<sup>+</sup>), 280, 249, 220, 202, 183, 165, 143, 116, 105, 89, 77.

**Compound (II-b-11)**

500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 2.25(1H, brs), 4.16(3H, s), 5.87(1H, brs), 5.93  
 (1H, d, J=1.0Hz), 5.94(1H, d, J=1.0Hz), 6.78(1H, d, J=7.8Hz), 6.88(1H, d  
 d, J=7.8, 1.0Hz), 7.10(1H, s), 7.42 (1H, dd, J=8.6, 1.0Hz), 7.47 (1H, d,  
 J=8.6Hz), 7.73 (1H, d, J=1.0Hz), 9.91 (1H, s).  
 MS(EI) m/e: 325(M<sup>+</sup>), 308, 277, 202, 172, 149, 122, 93.

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**Compound (II-b-12)**

500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 2.15 (1H, brs), 2.24 (3H, s), 2.32 (3H, s), 4.16 (3H, s), 6.08 (1H, brs), 6.99 (1H, brs), 7.07 (1H, brs), 7.08 (1H, brd, J=8.3Hz), 7.42 (1H, brd, J=8.3Hz), 7.42 (1H, brd, J=8.3Hz), 7.46 (1H, brd, J=8.3Hz), 7.64 (1H, brs), 9.90 (1H, s).

MS(EI) m/e: 309(M<sup>+</sup>), 293, 231, 219, 181, 169, 133, 131, 119, 104, 69.

**Compound (II-b-13)**

500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 2.30 (1H, brd, J=3.4Hz), 4.16 (3H, s), 5.94 (1H, brd, J=3.4Hz), 7.03 (2H, dd, J=8.6, 8.6Hz), 7.10 (1H, d, J=0.5Hz), 7.37 (2H, dd, J=10.5, 8.6Hz), 7.40 (1H, dd, J=8.5, 1.5Hz), 7.48 (1H, ddd, J=8.5, 0.7, 0.5Hz), 7.71 (1H, dd, J=1.5, 0.7Hz), 9.91 (1H, s).

MS(EI) m/e: 299(M<sup>+</sup>), 123.

**Compound (II-b-14)**

500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 2.24 (1H, brs), 3.80 (3H, s), 4.16 (3H, s), 5.92 (1H, s), 6.88 (2H, brd, J=8.8Hz), 7.10 (1H, d, J=0.9Hz), 7.31 (2H, brd, J=8.8Hz), 7.42 (1H, dd, J=8.8, 1.5Hz), 7.46 (1H, ddd, J=8.8, 0.9, 0.9Hz), 7.74 (1H, dd, J=1.5, 0.9Hz), 9.91 (1H, s).

MS(EI) m/e: 311(M<sup>+</sup>), 294, 263, 202, 135.

**Compound (II-b-15)**

400MHz  $^1\text{H-NMRR}$ (CDCl<sub>3</sub>),  $\delta$ : 2.53 (1H, brs), 4.18 (3H, s), 6.95-7.00 (2H, m), 7.12 (1H, brs), 7.26-7.32 (1H, m), 7.52 (2H, brs), 7.81 (1H, brs), 9.92 (1H, s).

MS(EI) m/e: 287(M<sup>+</sup>), 270, 239, 223, 202, 171, 143, 111.

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**Compound (II-b-16)**

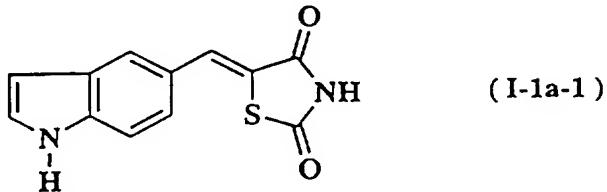
5 500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 0.18 (6H, s), 0.97 (9H, s), 2.27 (1H, brs), 4.16 (3H, s), 5.90 (1H, brs), 6.81 (2H, brd, J=8.5Hz), 7.09 (1H, d, J=0.5Hz), 7.23 (2H, brd, J=8.5Hz), 7.42 (1H, dd, J=8.9, 1.0Hz), 7.46 (1H, ddd, J=8.9, 0.5, 0.5Hz), 7.72 (1H, dd, J=1.0, 0.5Hz), 9.90 (1H, s).  
 MS(EI) m/e: 411(M<sup>+</sup>), 354, 323, 305, 294, 266, 235, 201, 150, 135.

**Compound (II-b-17)**

10 400MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 4.17 (3H, s), 7.10 (1H, brt, J=7.5Hz), 7.36 (2H, brt, J=7.5Hz), 7.54 (1H, d, J=0.9Hz), 7.73 (1H, dddd, J=8.8, 1.6, 0.9, 0.7Hz), 7.80 (2H, brd, J=7.5Hz), 8.07 (1H, dd, J=8.8, 1.6Hz), 8.49 (1H, dd, J=1.6, 0.7Hz), 9.99 (1H, s), 10.32 (1H, brs).  
 MS(EI) m/e: 294(M<sup>+</sup>), 202, 171, 143, 115, 92, 65.

**EXAMPLE 1**

15 **Synthesis of 5-(5-indolylmethylidene)thiazolidine-2,4-dione (Compound (I-1a-1)) (Step A)**



20

To a toluene (10 ml) solution of 548.7 mg (3.7800 mmol) of Compound (II-1), were added a toluene (0.5 ml) solution of 96.6 mg (1.134 mmol) of piperidine and 885.5 mg (7.56 mmol) of thiazolidine-2,4-dione and a toluene (0.5 ml) solution of 45.4 mg (0.756 mmol) of acetic acid, and the resultant mixture was heat-refluxed for 1 hour. Orange color crystals were precipitated from the reaction

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solution, and the crystals were filtrated and were dissolved in acetone. The solution thus obtained was heated with activated carbon, and methanol was added thereto and a solvent was then removed by distillation 5 under reduced pressure. Crystals precipitated were filtrated and dried to obtain 400.8 mg (43.4%) of the aimed material (compound (I-la-1)).

Yellow crystals

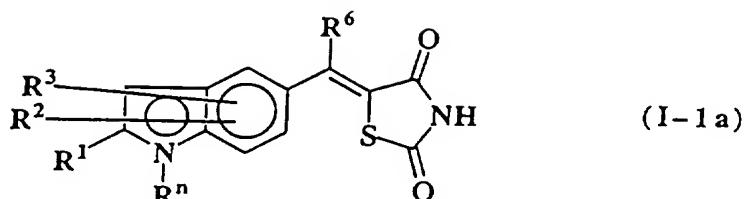
Melting point: 320-325°C (dec.) (solvent used for 10 recrystallization: methanol/acetone)

60MHz  $^1\text{H-NMR}$ (DMSO- $d_6$ ),  $\delta$ : 6.50(1H, m), 7.21(1H, dd,  $J=9.0, 2.0\text{Hz}$ ), 7.38(1H, d,  $J=5.0\text{Hz}$ ), 7.45(1H, d,  $J=9.0\text{Hz}$ ), 7.75(1H, d,  $J=2.0\text{Hz}$ ), 7.79(1H, s), 11.40(2H, brs).

MS(EI) m/e:244( $M^+$ ), 173, 145, 128.

15 In the same manner as above, the following compounds were synthesized ( $R^1$ ,  $R^2$ ,  $R^3$  and  $R^n$  and the table correspond to the substituents of Compound (I-la)).

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5

(R<sup>4</sup>,R<sup>7</sup>=bond, R<sup>6</sup>=H)

	Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting material (II)	Properties (mp °C)
10	I-1a-2	2-	H	H	H	II-a-2	Yellow powder (269-270, decomp.)
	I-1a-3	2-	H	H	H	II-a-3	Orange powder (265)
15	I-1a-4	2-	H	H	H	II-a-4	Yellow powder (315-318, decomp.)
	I-1a-5	2-	H	H	SO <sub>2</sub> Ph	II-a-5	Pale yellow powder (260, decomp.)

## Compound (I-1a-2)

500MHz <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>), δ: 4.09(2H, s), 6.28(1H, s), 7.20-7.35(6H, m), 7.20(1H, d, J=8.5Hz), 7.70(1H, d, J=1.0Hz), 7.85(1H, s), 11.38(1H, brs), 12.38(1H, brs).

MS(FAB<sup>+</sup>) m/e:335(M<sup>+</sup>), 263, 218.

## Compound (I-1a-3)

500MHz <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>), δ: 2.73(3H, s), 4.02(2H, s), 6.34(1H, s), 7.27(1H, dd, J=8.5, 1.0Hz), 7.45(1H, d, J=8.5Hz), 7.43-7.55(3H, m), 7.73(1H, d, J=1.0Hz), 7.86(1H, s), 7.92(2H, dd, J=5.8, 1.0Hz), 11.36(1H, brs), 12.43(1H, brs).

MS(EI) m/e:416(M<sup>+</sup>), 344, 172.

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**Compound (I-1a-4)**

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 2.66(3H, s), 7.54(1H, brt,  $J=8.0\text{Hz}$ ), 7.57(1H, d,  $J=8.8\text{Hz}$ ), 7.64(1H, brd,  $J=8.8\text{Hz}$ ), 7.67(2H, brt,  $J=8.0\text{Hz}$ ), 7.87(1H, s), 8.12(1H, s), 8.14(1H, s), 8.21(2H, brd,  $J=8.0\text{Hz}$ ), 12.31(1H, brs), 12.50  
5 (1H, brs).

MS(FD) m/e:429(M<sup>+</sup>).

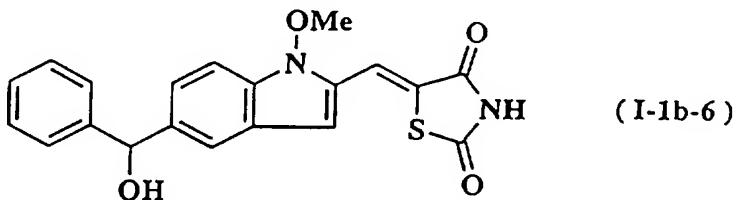
**Compound (I-1a-5)**

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 2.32(3H, s), 4.29(2H, s), 6.58(1H, s), 7.45-7.65(5H, m), 7.68(1H, t,  $J=7.0\text{Hz}$ ), 7.74(1H, d,  $J=1.0\text{Hz}$ ), 7.82(1H, s), 7.87  
10 -8.00(4H, m), 8.18(1H, d,  $J=8.8\text{Hz}$ ), 12.56(1H, brs).

MS(EI) m/e:555(M<sup>+</sup>), 414, 353, 141, 105.

To an ethanol (8 ml) solution of 494.7 mg (1.7586 mmol) of compound (II-b-6), were added 412.0 mg (3.5171 mmol) of thiazolidine-2,4-dione and 29.9 mg (0.3517 mmol) 15 of piperidine. A resultant mixture was heat-refluxed for 3 hours, and the reaction solution was cooled. Crystals precipitated were filtrated and dried to obtain 465.9 mg (69.6%) of the aimed compound (I-1b-6).

20



Yellow needle-like crystals

25 Melting point: 222-223°C (dec.) (solvent used for recrystallization: chloroform/ethanol)

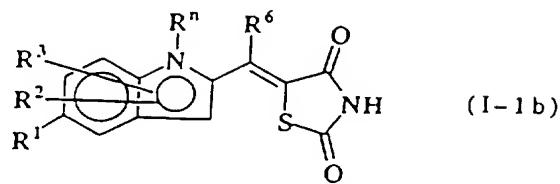
- 200 -

500MHz  $^1\text{H-NMR}$ (DMSO- $\text{d}_6$ ),  $\delta$ : 4.07(3H, s), 5.79(1H, d,  $J=3.9\text{Hz}$ ), 5.89(1H, d,  $J=3.9\text{Hz}$ ), 6.75(1H, s), 7.20(1H, brt,  $J=7.5\text{Hz}$ ), 7.30(2H, brt,  $J=7.5\text{Hz}$ ), 7.33(1H, dd,  $J=8.5, 1.0\text{Hz}$ ), 7.40(2H, brd,  $J=7.5\text{Hz}$ ), 7.48(1H, d,  $J=8.5\text{Hz}$ ), 7.69(1H, s), 7.71(1H, d).

5 MS(EI)  $m/e$ : 380( $\text{M}^+$ ), 349, 306, 205, 105.

In the same manner as above, the following compounds were synthesized ( $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^6$  and  $\text{R}^n$  correspond to the substituents of Compound (I-1b)).

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(R<sup>4</sup>,R<sup>7</sup>=bond , R<sup>6</sup>=H)

Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting material (II)	Properties (mp °C)
I-1b-7		H	H	MeO	II-b-7	Orange powder (226-227)
I-1b-8		H	H	MeO	II-b-8	Yellow crystals (260-265, decomp.)
I-1b-9		H	H	MeO	II-b-9	Orange powder (260-261, decomp.)
I-1b-10		H	H	MeO	II-b-10	Orange amorphous
I-1b-11		H	H	MeO	II-b-11	Orange powder (300-350, decomp.)
I-1b-12		H	H	MeO	II-b-12	Yellow powder (178-179, decomp.)
I-1b-13		H	H	MeO	II-b-13	Yellow needles (224-225, decomp.)

Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting material (II)	Properties (mp °C)
I-1b-14		H	H	MeO	II-b-14	Orange needles (219-220, decomp.)
5						
I-1b-15		H	H	MeO	II-b-15	Orange powder (>224, decomp.)
10						
I-1b-16		H	H	MeO	II-b-16	Yellow needles (111-113)
I-1b-17		H	H	MeO	II-b-17	Yellow powder (200-207, decomp.)

**Compound (I-1b-7)**

500MHz <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>), δ: 4.06(3H, s), 5.97(1H, d, J=3.0Hz), 6.05(1H, d, J=3.0Hz), 6.76(1H, s), 7.30-8.00(11H, m), 12.65(1H, brs).  
 15 MS(EI) m/e:430(M<sup>+</sup>), 301, 254, 220, 205, 155, 127, 91.

**Compound (I-1b-8)**

500MHz <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>), δ: 4.07(3H, s), 6.08(1H, d, J=3.4Hz), 6.25(1H, d, J=3.4Hz), 7.41(1H, s), 7.38-8.90(10H, m), 12.66(1H, brs).  
 20 MS(EI) m/e:431(M<sup>+</sup>), 400, 357, 330, 301, 255, 216, 200, 172, 156, 128.

**Compound (I-1b-9)**

500MHz <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>), δ: 2.62(3H, s), 4.18(3H, s), 7.07(1H, s), 7.50(1H, brt, J=7.6Hz), 7.63(2H, brt, J=7.6Hz), 7.71(1H, s), 7.74(1H, d, J=8.8Hz), 8.10(2H, brd, J=7.6Hz), 8.18(1H, dd, J=8.8, 1.0Hz), 8.78(1H, d, J=1.0Hz), 12.83(1H, brs).  
 25 MS(EI) m/e:459(M<sup>+</sup>), 385, 357, 225, 199, 171, 143, 127, 91.

## Compound (I-1b-10)

500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 3.05 (1H, brs), 4.09 (3H, s), 6.58 (1H, s), 7.20  
-7.50 (13H, m), 7.91 (1H, s), 8.90 (1H, brs).

MS(EI) m/e:456(M<sup>+</sup>), 379, 177, 149, 105, 77.

## 5 Compound (I-1b-11)

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 4.07 (3H, s), 5.71 (1H, d, J=4.0Hz), 5.84 (1H, d, J=4.0Hz), 5.94 (1H, d, J=0.5Hz), 5.95 (1H, d, J=0.5Hz), 6.75 (1H, s), 6.82 (1H, d, J=8.9Hz), 6.87 (1H, dd, J=8.9, 1.0Hz), 6.90 (1H, d, J=1.0Hz), 7.32 (1H, dd, J=8.5, 1.0Hz), 7.47 (1H, d, J=8.5Hz), 7.69 (2H, s), 12.65 (1H, brs).

10 65 (1H, brs).

MS(EI) m/e:424(M<sup>+</sup>), 228, 213, 102.

## Compound (I-1b-12)

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 2.16 (3H, s), 2.24 (3H, s), 4.07 (3H, s), 5.69 (1H, d, J=3.8Hz), 5.87 (1H, d, J=3.8Hz), 6.75 (1H, s), 6.91 (1H, brs),

15 7.01 (1H, brd, J=7.6Hz), 7.26 (1H, dd, J=8.5, 1.0Hz), 7.39 (1H, d, J=7.6Hz), 7.47 (1H, d, J=8.5Hz), 7.58 (1H, brs), 7.69 (1H, s), 12.65 (1H, brs).

MS(EI) m/e:408(M<sup>+</sup>), 379, 358, 275, 205, 172, 133, 105.

## Compound (I-1b-13)

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 4.07 (3H, s), 5.80 (1H, d, J=3.8Hz), 5.96 (1H, d, J=3.8Hz), 6.75 (1H, s), 7.12 (2H, t, J=8.3Hz), 7.32 (1H, dd, J=8.6, 1.2Hz), 7.42 (2H, dd, J=8.3, 5.7Hz), 7.48 (1H, d, J=8.6, 0.5Hz), 7.70 (1H, dd, J=1.2, 0.5Hz), 12.65 (1H, brs).

20 MS(FAB<sup>+</sup>) m/e:398(M<sup>+</sup>).

## Compound (I-1b-14)

25 500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 3.38 (3H, s), 4.07 (3H, s), 5.74 (1H, d, J=3.8Hz), 5.80 (1H, d, J=3.8Hz), 6.74 (1H, brs), 6.85 (2H, d, J=8.8Hz), 7.28 (2H, d, J=8.8Hz), 7.31 (1H, dd, J=8.6, 1.0Hz), 7.47 (1H, dd, J=8.6, 0.5Hz), 7.68 (1H, dd, J=1.0, 0.5Hz), 7.69 (1H, s), 12.65 (1H, brs).

MS(EI) m/e:410(M<sup>+</sup>), 220, 205, 172, 135, 108, 77.

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**Compound (I-1b-15)**

500MHz  $^1\text{H-NMR}$ (DMSO- $d_6$ ),  $\delta$ : 4.09 (3H, s), 6.02 (1H, d,  $J=4.5\text{Hz}$ ), 6.23 (1H, d,  $J=4.5\text{Hz}$ ), 6.78 (1H, s), 6.88 (1H, dd,  $J=4.0, 0.4\text{Hz}$ ), 6.92 (1H, dd,  $J=5.0, 4.0\text{Hz}$ ), 7.38 (1H, dd,  $J=5.0, 0.4\text{Hz}$ ), 7.40 (1H, dd,  $J=8.6, 0.3\text{Hz}$ ), 7.51 (1H, d,  $J=8.6\text{Hz}$ ), 7.70 (1H, s), 7.75 (1H, d,  $J=0.3\text{Hz}$ ), 12.65 (1H, brs).

MS(EI)  $m/e$ : 386( $M^+$ ), 301, 256, 205, 171, 145, 111, 85.

**Compound (I-1b-16)**

400MHz  $^1\text{H-NMR}$ (DMSO- $d_6$ ),  $\delta$ : 0.15 (6H, s), 0.93 (9H, s), 4.07 (3H, s), 5.72 (1H, d,  $J=3.7\text{Hz}$ ), 5.82 (1H, d,  $J=3.7\text{Hz}$ ), 6.75 (1H, s), 6.77 (2H, d,  $J=8.4\text{Hz}$ ), 7.25 (2H, d,  $J=8.4\text{Hz}$ ), 7.32 (1H, brd,  $J=8.3\text{Hz}$ ), 7.47 (1H, brd,  $J=8.3\text{Hz}$ ), 7.68 (1H, s), 7.69 (1H, brs), 12.09 (1H, brs).

MS(EI)  $m/e$ : 510( $M^+$ ), 422, 378, 205.

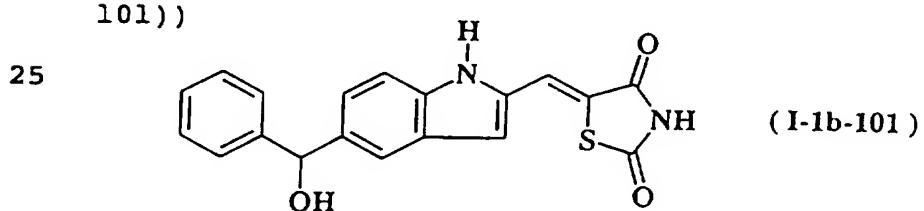
**Compound (I-1b-17)**

15 400MHz  $^1\text{H-NMR}$ (DMSO- $d_6$ ),  $\delta$ : 4.17 (3H, s), 6.93 (1H, s), 7.11 (1H, brt,  $J=7.3\text{Hz}$ ), 7.35 (2H, brt,  $J=7.3\text{Hz}$ ), 7.69 (1H, d,  $J=8.8\text{Hz}$ ), 7.72 (1H, s), 7.80 (2H, brd,  $J=7.3\text{Hz}$ ), 7.96 (1H, d,  $J=8.8\text{Hz}$ ), 8.40 (1H, brs), 10.28 (1H, brs), 12.70 (1H, brs).

MS(EI)  $m/e$ : 393( $M^+$ ), 301, 270, 230, 199, 171, 127, 92, 65.

**20 EXAMPLE 2****Removal of substituent  $R^n$  (Step C)**

Synthesis of 5-((5-(1-hydroxybenzyl)indole-2-yl)methylidene)thiazolidine-2,4-dione (Compound (I-1b-101))



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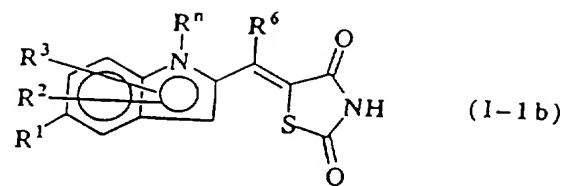
To a tetrahydrofuran-water (12 ml-4 ml) solution of 455.9 mg (1.1984 mmol) of compound (I-1b-6), were added 489.1 mg of magnesium oxide and 476.8 mg of 10% Pd-C, and the resultant mixture was stirred for 20 hours at room 5 temperature under hydrogen atmosphere of 1 atmospheric pressure. After terminating the reaction, the reducing agent was removed by filtration. The solvent in the filtrate was removed by distillation under reduced pressure, and a residue obtained was recrystallized to 10 obtain 409.4 mg (97.5%) of the subject compound (I-1b-101).

Yellow powder

Melting point: 450°C< (solvent used for  
recrystallization: THF/benzene)

15 500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$  : 5.77(1H, d,  $J=3.9\text{Hz}$ ), 5.82(1H, d,  $J=3.9\text{Hz}$ ), 6.77(1H, s,), 7.18 (1H, brt,  $J=9.0\text{Hz}$ ), 7.21(1H, d,  $J=9.0\text{Hz}$ ), 7.28(2H, brt,  $J=9.0\text{Hz}$ ), 7.36(1H, d,  $J=9.0\text{Hz}$ ), 7.39(2H, brd,  $J=9.0\text{Hz}$ ), 7.65(1H, s), 7.72(1H, s), 11.59(1H, brs), 12.52(1H, brs).  
MS(EI) m/e:350(M<sup>+</sup>), 279, 220, 205, 145, 105, 91, 77.

20 In the same manner as above, the following compounds were synthesized (R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>n</sup> in the table correspond to the substituents of Compound (I-1b)).



(R<sup>4</sup>,R<sup>7</sup>=bond , R<sup>6</sup>=H)

Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting material (I-1b)	Properties (mp °C)
I-1b-102		H	H	H	I-1b-11	Yellow powder (330-400, decomp.)
I-1b-103		H	H	H	I-1b-12	Yellow powder (125-160, decomp.)
I-1b-104		H	H	H	I-1b-13	Yellow powder (246-250, decomp.)
I-1b-105		H	H	H	I-1b-14	Yellowish orange powder (280-300, decomp.)
I-1b-106		H	H	H	I-1b-15	Yellow powder (280-290, decomp.)

**Compound (I-1b-102)**

500MHz  $^1\text{H-NMR}$ (DMSO- $\text{d}_6$ ),  $\delta$ : 5.68 (1H, d,  $J=3.9\text{Hz}$ ), 5.77 (1H, d,  $J=3.9\text{Hz}$ ), 5.93 (1H, d,  $J=0.5\text{Hz}$ ), 5.95 (1H, d,  $J=0.5\text{Hz}$ ), 6.78 (1H, d,  $J=1.0\text{Hz}$ ), 6.81 (1H, d,  $J=8.0\text{Hz}$ ), 6.86 (1H, dd,  $J=8.0, 1.0\text{Hz}$ ), 6.89 (1H, d,  $J=1.0\text{Hz}$ ), 7.20 (1H, dd,  $J=8.6, 1.0\text{Hz}$ ), 7.36 (1H, d,  $J=8.6\text{Hz}$ ), 7.63 (1H, d,  $J=1.0\text{Hz}$ ), 7.74 (1H, s), 11.59 (1H, s), 12.50 (1H, brs).

MS(FD $^+$ ) m/e:394(M $^+$ ).

**Compound (I-1b-103)**

500MHz  $^1\text{H-NMR}$ (DMSO- $\text{d}_6$ ),  $\delta$ : 2.14 (3H, s), 2.24 (3H, s), 5.62 (1H, d,  $J=5.0\text{Hz}$ ), 5.86 (1H, d,  $J=5.0\text{Hz}$ ), 6.77 (1H, s), 6.90 (1H, s), 7.01 (1H, brd,  $J=6.9\text{Hz}$ ), 7.14 (1H, brd,  $J=8.1\text{Hz}$ ), 7.36 (1H, d,  $J=8.1\text{Hz}$ ), 7.39 (1H, d,  $J=6.9\text{Hz}$ ), 7.52 (1H, s), 7.73 (1H, s), 11.59 (1H, brs), 12.50 (1H, brs).

MS(FAB $^+$ ) m/e:379(M $^++1$ ), 362.

**Compound (I-1b-104)**

500MHz  $^1\text{H-NMR}$ (DMSO- $\text{d}_6$ ),  $\delta$ : 5.78 (1H, d,  $J=3.8\text{Hz}$ ), 5.89 (1H, d,  $J=3.8\text{Hz}$ ), 6.78 (1H, dd,  $J=1.0, 0.3\text{Hz}$ ), 7.11 (2H, t,  $J=9.0\text{Hz}$ ), 7.20 (1H, dd,  $J=5.1, 1.0\text{Hz}$ ), 7.37 (1H, dd,  $J=5.1, 0.5, 0.3\text{Hz}$ ), 7.40 (2H, dd,  $J=9.0, 6.1\text{Hz}$ ), 7.65 (1H, dd,  $J=1.0, 0.5\text{Hz}$ ), 7.74 (1H, s), 11.61 (1H, brs), 12.52 (1H, brs).

MS(FAB $^+$ ) m/e:368(M $^++1$ ).

**20 Compound (I-1b-105)**

500MHz  $^1\text{H-NMR}$ (DMSO- $\text{d}_6$ ),  $\delta$ : 3.71 (3H, s), 5.71 (1H, d,  $J=3.8\text{Hz}$ ), 5.73 (1H, d,  $J=3.8\text{Hz}$ ), 6.78 (1H, dd,  $J=1.0, 0.5\text{Hz}$ ), 6.85 (2H, d,  $J=8.5\text{Hz}$ ), 7.19 (1H, dd,  $J=8.5, 1.0\text{Hz}$ ), 7.27 (2H, d,  $J=8.5\text{Hz}$ ), 7.35 (1H, ddd,  $J=8.5, 0.5, 0.5\text{Hz}$ ), 7.63 (1H, dd,  $J=1.0, 0.5\text{Hz}$ ), 7.74 (1H, s), 11.59 (1H, brs), 12.50 (1H, brs).

MS(FAB $^+$ ) m/e:381(M $^++1$ ), 380, 363.

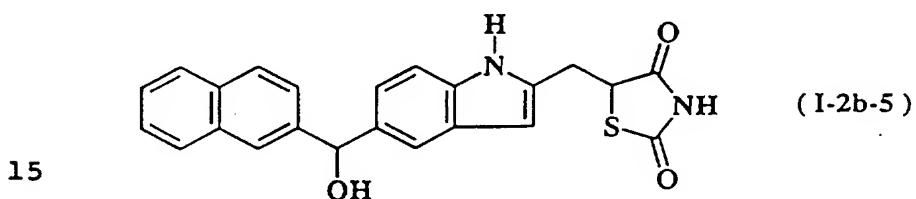
- 208 -

## Compound (I-1b-106)

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$  : 5.99 (1H, d,  $J=4.2\text{Hz}$ ), 6.16 (1H, d,  $J=4.2\text{Hz}$ ), 6.81 (1H, dd,  $J=1.0, 0.5\text{Hz}$ ), 6.85 (1H, dd,  $J=4.0, 1.0\text{Hz}$ ), 6.92 (1H, dd,  $J=5.1, 4.0\text{Hz}$ ), 7.28 (1H, dd,  $J=8.8, 1.0\text{Hz}$ ), 7.37 (1H, dd,  $J=5.1, 1.0\text{Hz}$ ), 7.40 (1H, ddd,  $J=8.8, 0.7, 0.5\text{Hz}$ ), 7.69 (1H, dd,  $J=1.0, 0.5\text{Hz}$ ), 7.75 (1H, s), 11.64 (1H, brs), 12.52 (1H, brs).

MS(EI) m/e:356(M<sup>+</sup>), 340, 286, 269, 245, 174, 143, 116, 99, 44.

Compound (I-1b-7) was reduced in the same manner as above, and compound (I-2b-5) wherein the substituent R<sup>n</sup> 10 was removed and the connecting part between an indole ring and a thiazole ring was reduced, was formed.



Light-yellow powder

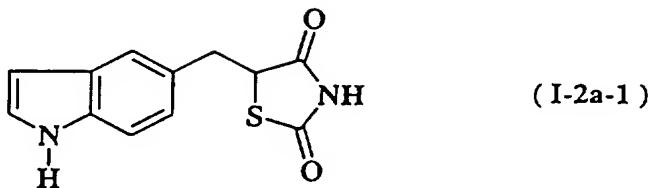
Melting point: 100-108°C (solvent used for recrystallization: chloroform/hexane)

20 500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$  : 3.26(1H, dd,  $J=15.4, 9.8\text{Hz}$ ), 3.50(1H, dd,  $J=15.4, 3.9\text{Hz}$ ), 4.94(1H, dd,  $J=9.8, 3.9\text{Hz}$ ), 5.82(1H, d,  $J=3.9\text{Hz}$ ), 5.90(1H, d,  $J=3.9\text{Hz}$ ), 6.18(1H, s), 7.00-8.00(10H, m), 10.97(1H, s), 12.07(1H, brs).

## EXAMPLE 3

25 Synthesis of 5-(indole-ylmethyl)thiazolidine-2,4-dione (Compound (I-2a-1)) (Step B)

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**EXAMPLE 3-1 Reduction by hydrogenation**

To a tetrahydrofuran (10 ml) solution of 104.7 mg (0.4286 mmol) of compound (I-1a-1), was added 109.7 mg of 10% Pd-C, and the resultant mixture was stirred at room 10 temperature for 20 hours under hydrogen atmosphere of 1 atmospheric pressure. After finishing the reaction, the reducing agent was removed by filtration. The solvent in the filtrate was removed by distillation under reduced pressure, and a residue obtained was dissolved in a 15 solvent of ethyl acetate/hexane (1/1). This solution was filtrated by silica gel, and was subjected to recrystallization to obtain 80.8 mg of the aimed compound (I-2a-1).

Yellow column-like crystals

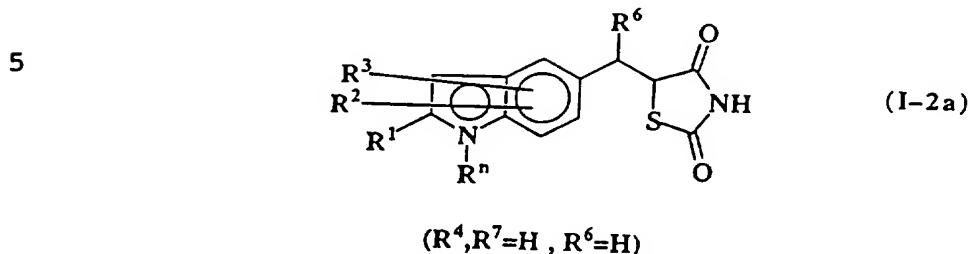
20 Melting point: 159.5-160.5°C (solvent used for recrystallization: ethylacetate/hexane)

60MHz  $^1\text{H-NMR}$ (CD<sub>3</sub>COCD<sub>3</sub>),  $\delta$  : 3.15(1H, dd, J=12.0, 9.0Hz), 3.60(1H, dd, J=12.0, 5.0Hz), 4.70(1H, dd, J=9.0, 5.0Hz), 6.31(1H, m), 6.90-7.60(4H, m), 10.00(1H, brs).

25 MS(EI) m/e:246(M<sup>+</sup>), 130, 115.

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In the same manner as above, the following compounds were synthesized ( $R^1$ ,  $R^2$ ,  $R^3$  and  $R^n$  in the table correspond to the substituents of Compound (I-2a)).



	Compound No.	$R^1$	$R^2$	$R^3$	$R^n$	Starting material (I-1a)	Properties (mp °C)
10	I-2a-2	2-	H	H	H	I-1a-2	Yellow prisms (132-133)
15	I-2a-3	2-	H	H	H	I-1a-3	Pale yellow powder (111-112)
20	I-2a-4	2-	H	H	$SO_2Ph$	I-1a-5	Pale yellow prisms (104-105)
	I-2a-7	2-	H	H	H	I-1a-4	Pale yellow crystals (115-116)

#### Compound (I-2a-2)

500MHz  $^1H$ -NMR ( $CDCl_3$ ),  $\delta$ : 3.19(1H, dd,  $J=14.1$ , 10.1Hz), 3.63(1H, dd,  $J=14.1$ , 3.9Hz), 4.13(2H, s), 4.57(1H, dd,  $J=10.1$ , 3.9Hz), 6.30(1H, dd,  $J=1.0$ , 0.5Hz), 6.97(1H, dd,  $J=8.3$ , 1.7Hz), 7.20(1H, ddd,  $J=8.3$ , 0.5, 0.5Hz), 7.21-7.27(5H, m), 7.39(1H, dd,  $J=0.5$ , 0.5Hz), 7.77 (1H, brs), 7.79 (1H, br s).

MS(FAB $^+$ ) m/e:337( $M^+$ ), 220.

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**Compound (I-2a-3)**

500MHz  $^1\text{H-NMR}$ (DMSO- $\text{d}_6$ ),  $\delta$  : 2.35(3H, s), 3.10(1H, dd,  $J=7.5, 5.0\text{Hz}$ ), 3.42(1H, dd,  $J=7.5, 2.5\text{Hz}$ ), 3.97(2H, s), 4.88(1H, dd,  $J=5.0, 2.5\text{Hz}$ ), 6.14(1H, s), 6.89(1H, dd,  $J=8.0, 1.0\text{Hz}$ ), 7.23(1H, d,  $J=8.0\text{Hz}$ ), 7.27(1H, d,  $J=1.0\text{Hz}$ ), 7.45-7.55(3H, m), 7.91(2H, dd,  $J=8.0, 2.0\text{Hz}$ ), 10.90(1H, brs), 11.96(1H, brs).

MS(FAB $^+$ )  $m/e$ :418( $M^+$ ), 301, 172.

**Compound (I-2a-4)**

10 500MHz  $^1\text{H-NMR}$ (CDCl $_3$ ),  $\delta$  : 2.30(3H, s), 3.18(1H, dd,  $J=15.0, 10.0\text{Hz}$ ), 3.56(1H, dd,  $J=15.0, 5.0\text{Hz}$ ), 4.25(2H, s), 4.52(1H, dd,  $J=10.0, 5.0\text{Hz}$ ), 6.31(1H, s), 7.12(1H, dd,  $J=8.0, 2.0\text{Hz}$ ), 7.30-7.50(6H, m), 7.52(1H, dd,  $J=8.0, 8.0\text{Hz}$ ), 7.78(2H, dd,  $J=7.0, 1.0\text{Hz}$ ), 7.82(1H, brs), 7.97-8.02(2H, m), 8.11(1H, d,  $J=8.0\text{Hz}$ ).

15 MS(EI)  $m/e$ :557( $M^+$ ), 416, 386, 299.

**Compound (I-2a-7)**

500MHz  $^1\text{H-NMR}$ (CDCl $_3$ ),  $\delta$  : 2.65 (3H, s), 3.21 (1H, dd,  $J=14.2, 8.8\text{Hz}$ ), 3.48(1H, dd,  $J=14.2, 4.4\text{Hz}$ ), 4.95 (1H, dd,  $J=8.8, 4.4\text{Hz}$ ), 7.23 (1H, brd,  $J=8.5$ ), 7.46 (1H, brd,  $J=8.5\text{Hz}$ ), 7.52 (1H, brt,  $J=7.6\text{Hz}$ ), 7.66 (1H, brs), 7.97 (1H, brs), 8.20 (1H, brt,  $J=7.6\text{Hz}$ ), 11.96 (1H, brs), 12.01 (1H, brs).

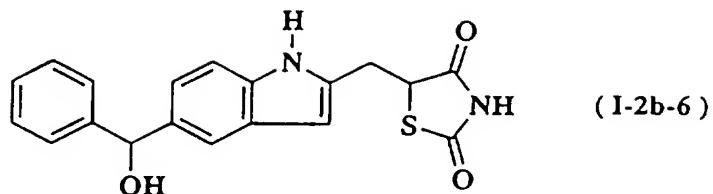
MS(EI)  $m/e$ :431( $M^+$ ), 415, 205, 183, 156, 129, 91.

**EXAMPLE 3-2 Reduction by amalgam**

**Synthesis of 5-((5-(1-hydroxybenzyl)indole-2-**

25 **yl)methyl)thiazolidine-2,4-dione (Compound (I-2a-6))**

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To a MeOH (3 ml) solution of 119.0 mg (0.3396 mmol) of compound (I-1b-6), was added 3% sodium-amalgam, and the resultant mixture was stirred at room temperature for 18 hours. After finishing the reaction, the reaction 10 mixture was filtrated to remove the reducing agent. The solvent in the filtrate was removed by distillation under reduced pressure, and a residue obtained was subjected to silica gel column chromatography (eluent: tetrahydrofuran/benzene=1/3) to obtain 86.0 mg (61.1%) of 15 the subject compound (I-2b-6).

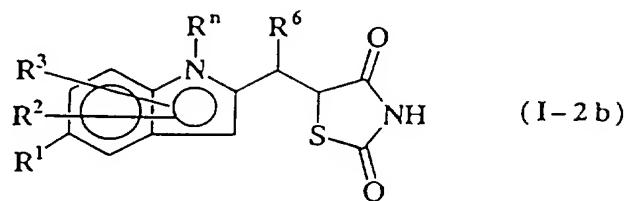
Colorless powder

Melting point: 84-87°C (solvent used for recrystallization: chloroform/hexane)

500MHz  $^1\text{H-NMR}$ (CDCl<sub>3</sub>),  $\delta$ : 3.42(1H, dd, J=15.4, 7.3Hz), 3.53(1H, dd, J=15.4, 4.9Hz), 4.60(1H, dd, J=7.3, 4.9Hz), 5.95(1H, d, J=2.0Hz), 6.35(1H, d, J=7.8Hz), 7.25(1H, brt, J=7.6Hz), 7.28(1H, d, J=7.6Hz), 7.33(2H, brt, J=7.6Hz), 7.42(2H, brd, J=7.6Hz), 7.56(1H, s), 7.95(1H, brs), 8.26(1H, brs). MS(EI) m/e: 352(M<sup>+</sup>), 236, 205, 105, 78.

In the same manner as above, the following compounds 25 were synthesized (R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>n</sup> in the table correspond to the substituents of Compound (I-2b)).

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(R<sup>4</sup>,R<sup>7</sup>=bond , R<sup>6</sup>=H)

Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting material (I-1b)	Properties (mp °C)
I-2 b-8		H	H	H	I-1b-102	Pale yellow amorphous
I-2 b-9		H	H	H	I-1b-103	Yellow powder (102-104)
I-2 b-10		H	H	H	I-1b-104	Pale yellow powder (77-81)
I-2 b-11		H	H	H	I-1b-105	Pale yellow powder (75-77, decomp.)
I-2 b-12		H	H	H	I-1b-106	Pale yellow powder (68-69, decomp.)

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**Compound (I-2b-8)**

500MHz  $^1\text{H-NMR}$  (DMSO- $\text{d}_6$ ),  $\delta$  : 3.25 (1H, dd,  $J=15.2, 10.0\text{Hz}$ ), 3.51 (1H, dd,  $J=15.2, 3.6\text{Hz}$ ), 4.94 (1H, dd,  $J=10.0, 3.6\text{Hz}$ ), 5.63 (1H, d,  $J=4.5\text{Hz}$ ), 5.64 (1H, d,  $J=4.5\text{Hz}$ ), 5.92 (1H, brs), 5.93 (1H, brs), 6.18 (1H, brs), 6.79 5 (1H, d,  $J=8.0\text{Hz}$ ), 6.83 (1H, dd,  $J=8.0, 1.0\text{Hz}$ ), 6.88 (1H, d,  $J=1.0\text{Hz}$ ), 7.01 (1H, brd,  $J=8.5\text{Hz}$ ), 7.20 (1H, brd,  $J=8.5\text{Hz}$ ), 7.41 (1H, brs), 10.96 (1H, brs), 12.07 (1H, brs).

MS(EI)  $m/e: 396(M^++1)$ , 280, 149.

**Compound (I-2b-9)**

10 500MHz  $^1\text{H-NMR}$  (DMSO- $\text{d}_6$ ),  $\delta$  : 2.12 (3H, s), 2.23 (3H, s), 3.24 (1H, dd,  $J=17.5, 9.5\text{Hz}$ ), 3.51 (1H, dd,  $J=17.5, 5.0\text{Hz}$ ), 4.95 (1H, dd,  $J=9.5, 5.0\text{Hz}$ ), 5.46 (1H, d,  $J=4.5\text{Hz}$ ), 5.81 (1H, d,  $J=4.5\text{Hz}$ ), 6.16 (1H, brs), 6.88 (1H, brs), 6.95 (1H, brd,  $J=8.0\text{Hz}$ ), 6.99 (1H, brd,  $J=8.0\text{Hz}$ ), 7.20 (1H, brd,  $J=8.0\text{Hz}$ ), 7.31 (1H, brs), 7.41 (1H, brd,  $J=8.0\text{Hz}$ ), 10.97 (1H, brs), 12.09 (brs).

15 MS(FAB $^+$ )  $m/e: 381(M^++1)$ , 364.

**Compound (I-2b-10)**

500MHz  $^1\text{H-NMR}$  (DMSO- $\text{d}_6$ ),  $\delta$  : 3.27 (1H, dd,  $J=15.4, 9.8\text{Hz}$ ), 3.51 (1H, dd,  $J=15.4, 4.2\text{Hz}$ ), 4.95 (1H, dd,  $J=9.8, 4.2\text{Hz}$ ), 5.73 (1H, d,  $J=3.9\text{Hz}$ ), 5.75 20 (1H, d,  $J=3.9\text{Hz}$ ), 6.18 (1H, brs), 7.00 (1H, brd,  $J=8.3\text{Hz}$ ), 7.08 (2H,  $J=8.8\text{Hz}$ ), 7.21 (1H, brd,  $J=8.3\text{Hz}$ ), 7.39 (2H, dd,  $J=8.8, 5.8\text{Hz}$ ), 7.42 (1H, brs), 10.89 (1H, brs), 12.09 (1H, brs).

MS(FAB $^+$ )  $m/e: 371(M^++1)$ , 370, 353, 307, 254.

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Compound (I-2b-11)

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 3.70 (3H, s), 5.58 (1H, d,  $J=3.9\text{Hz}$ ), 5.67 (1H, d,  $J=3.9\text{Hz}$ ), 6.17 (1H, brs), 6.83 (2H, d,  $J=9.5\text{Hz}$ ), 7.00 (1H, brd,  $J=4.3\text{Hz}$ ), 7.20 (1H, brd,  $J=4.3\text{Hz}$ ), 7.26 (2H, d,  $J=9.5\text{Hz}$ ), 7.40 (1H, brs), 10.96 (1H, brs), 12.07 (1H, brs).

MS(FAB $^+$ ) m/e:382(M $^+$ ), 365, 266, 249, 135, 119.

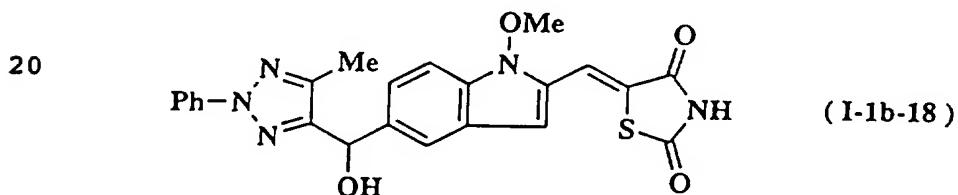
Compound (I-2b-12)

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 3.27 (1H, dd,  $J=15.0, 10.0\text{Hz}$ ), 3.52 (1H, dd,  $J=15.0, 3.9\text{Hz}$ ), 4.96 (1H, dd,  $J=10.0, 3.9\text{Hz}$ ), 5.94 (1H, d,  $J=4.2\text{Hz}$ ), 6.02 (1H, d,  $J=4.2\text{Hz}$ ), 6.20 (1H, brs), 6.82 (1H, dd,  $J=3.4, 1.2\text{Hz}$ ), 6.90 (1H, dd,  $J=5.3, 3.4\text{Hz}$ ), 7.09 (1H, brd,  $J=8.3\text{Hz}$ ), 7.25 (1H, brd,  $J=8.3\text{Hz}$ ), 7.33 (1H, dd,  $J=5.3, 1.2\text{Hz}$ ), 7.48 (1H, brs), 11.03 (1H, brs), 12.10 (1H, brs).

MS(FAB $^+$ ) m/e:358(M $^+$ ), 341, 242.

15 EXAMPLE 4

Synthesis of 5-((1-methoxy-5-hydroxy(2-phenyl-5-methyl-1,2,3-triazol-4-yl)methylindol-2-yl)methylidenethiazolidine-2,4-dione (Compound (I-1b-18))



To a tetrahydrofuran (5 ml) solution of 129.8 mg (0.2825 mmol) of compound (I-1b-9), was added 21.4 mg (0.5650 mmol) of sodium borohydride at room temperature, and the resultant mixture was stirred for 1 hour. After finishing the reaction, water and 2M hydrochloric acid

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were added to the reaction solution and the reaction solution was extracted with a mixed solvent of chloroform: MeOH=9:1. An organic phase obtained was washed with a saturated sodium chloride aqueous solution, 5 and a solvent was removed by distillation under reduced pressure. A residue obtained was recrystallized from chloroform/hexane to obtain 127.9 mg (98.1%) of Compound (I-1b-18).

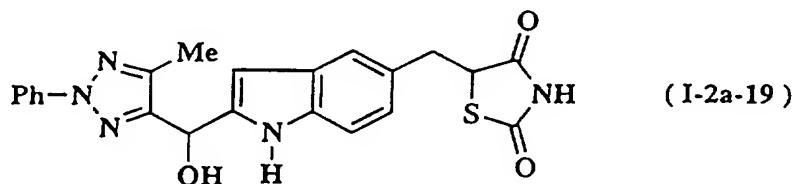
Orange crystals

10 Melting point: 170-176°C (decomposition) (solvent used for recrystallization: chloroform/hexane)

500MHz  $^1\text{H-NMR}$ (DMSO-d<sub>6</sub>),  $\delta$ : 2.21 (3H, s), 4.07 (3H, s), 6.08 (1H, d,  $J$ =4.3 Hz), 6.19 (1H, d,  $J$ =4.3Hz), 6.79 (1H, s), 7.35 (1H, brt,  $J$ =7.5Hz), 7.40 (1H, d,  $J$ =8.0Hz), 7.53 (2H, brt,  $J$ =7.5Hz), 7.45 (1H, d,  $J$ =8.0Hz), 7.68 (1H, s), 7.27 (1H, brs), 7.93 (2H, brt,  $J$ =7.5Hz), 12.63 (1H, brs).  
15 MS(EI) m/e:461(M<sup>+</sup>), 431, 387, 362, 331, 301, 186, 172, 117.

EXAMPLE 5

Synthesis of 5-((2-hydroxy(2-phenyl-5-methyl-1,2,3-tiazol-4-yl)methylindol-5-yl)methyl)thiazolidine-2,4-dione (Compound (I-2a-19))



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To a tetrahydrofuran (3 ml) solution of 100.5 mg (0.2329 mmol) of Compound (I-2a-7), was added 26.4 mg

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(0.6988 mmol) of sodium borohydride at room temperature, and the resultant mixture was stirred for 3 hours. After finishing the reaction, water and 2M hydrochloric acid were added to the reaction solution and the reaction 5 solution was extracted with a mixed solvent of chloroform: MeOH=9:1. An organic layer obtained was washed with a saturated sodium chloride aqueous solution, and a solvent was removed by filtration under reduced pressure. A residue obtained was recrystallized with 10 chloroform-hexane, and the recrystallized material was subjected to silica gel column chromatography (eluent: tetrahydrofuran/hexane = 1/2) and was further recrystallized from chloroform-hexane to obtain 14.8 mg (14.7%) of Compound (I-2a-19).

15 Colorless crystals

Melting point: 103-108°C(decomposition) (solvent used for recrystallization: chloroform/hexane)

500MHz  $^1\text{H-NMR}$ (DMSO- $\text{d}_6$ ),  $\delta$ : 3.10 (1H, dd,  $J=14.0, 9.8\text{Hz}$ ), 3.44 (1H, dd,  $J=14.1, 4.2\text{Hz}$ ), 4.89 (1H, dd,  $J=9.8, 4.2\text{Hz}$ ), 6.13 (1H, d,  $J=4.6\text{Hz}$ ), 6.22 20 (1H, brs), 6.28 (1H, d,  $J=4.6\text{Hz}$ ), 6.93 (1H, brd,  $J=8.3\text{Hz}$ ), 7.28 (1H, brd,  $J=8.3\text{Hz}$ ), 7.32 (1H, brs), 7.73 (1H, brt,  $J=7.8\text{Hz}$ ), 7.53 (2H, brt,  $J=7.8\text{Hz}$ ), 7.95 (2H, brd,  $J=7.8\text{Hz}$ ), 11.05 (1H, brs), 11.97 (1H, brs). MS(EI) m/e:433( $\text{M}^+$ ), 315, 299, 187, 158, 130.

25 20 mg (0.0479 mmol) of Compound (I-2a-3) was dissolved in 2 ml of a methanol/tetrahydrofuran mixture solution (1/1 v/v). 2.57 ml of sodium hydroxide aqueous solution (74.7 mg%) was added to the above prepared

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solution of Compound (I-2a-3), and the resultant mixture was stirred at room temperature for 1 hour and 20 minutes. Thereafter, a solvent was removed by distillation under reduced pressure and an aqueous 5 solution of a residue obtained was freeze-dried to obtain 16.4 mg (77.9%) of Compound (I-4a-1).

Colorless crystals

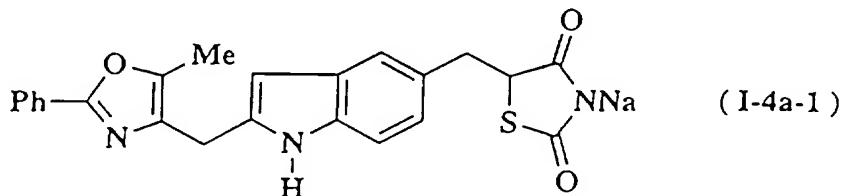
Melting point: 260-265°C (decomposition)

MS(FAB<sup>+</sup>) m/e: 439(M<sup>+</sup>)

10 EXAMPLE 6

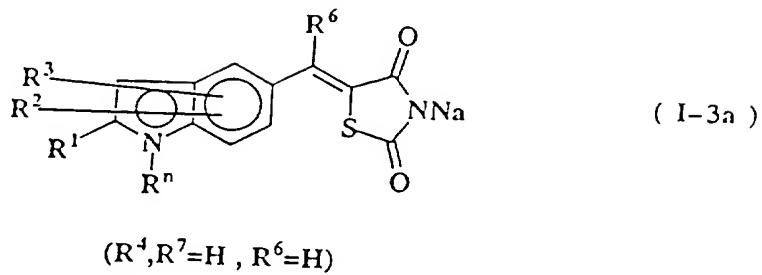
Preparation of sodium salt of 5-(((2-phenyl-5-methyl-1,2,3-triazol-4-yl)methylindol-5-yl)methyl)thiazolidine-2,4-dione (Compound (I-4a-1))

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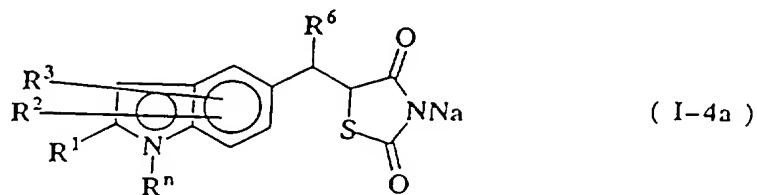
In the same manner as above, the following compounds 20 were synthesized (R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>n</sup> in the table correspond to the substituents of Compounds (I-3a, I-4a, I-3b and I-4b)).

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Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting materials (I-1a)	Properties (mp °C)
I-3a-1	2-	H	H	SO <sub>2</sub> Ph	I-1a-5	Colorless amorphous (160-180, decomp.)

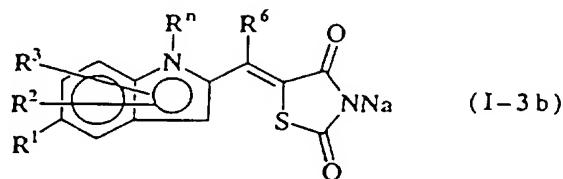
Compound (I-3a-1)

MS(FAB<sup>+</sup>) m/e: 578 (M<sup>+</sup>+1).(R<sup>4</sup>, R<sup>7</sup>=H, R<sup>6</sup>=H)

Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting materials (I-2a)	Properties (mp °C)
I-4a-2	2-	H	H	H	I-2a-7	Yellow powder (180-250, decomp.)

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## Compound (I-4a-2)

MS(FD) m/e: 476(M<sup>+</sup>+Na), 454(M<sup>+</sup>+1), 431(M<sup>+</sup>-Na+1).(R<sup>4</sup>,R<sup>7</sup>=bond, R<sup>6</sup>=H)

Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting materials (I-1b)	Properties (mp °C)
I-3b-2		H	H	MeO	I-1b-6	Yellow amorphous (220-230, decomp.)
I-3b-3		H	H	MeO	I-1b-7	Yellow amorphous (260-280, decomp.)
I-3b-4		H	H	MeO	I-1b-8	Yellow amorphous (195-230, decomp.)
I-3b-5		H	H	MeO	I-1b-11	Yellow amorphous (180-230, decomp.)
I-3b-6		H	H	MeO	I-1b-13	Yellow amorphous (172-176, decomp.)
I-3b-7		H	H	MeO	I-1b-14	Yellow amorphous (164-170, decomp.)
I-3b-8		H	H	MeO	I-1b-15	Yellow amorphous (240-260, decomp.)

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Compound (I-3a-2)

MS(FAB<sup>+</sup>) m/e: 403(M<sup>+</sup>+1).

Compound (I-3a-3)

MS(FAB<sup>+</sup>) m/e: 403(M<sup>+</sup>+1).

5 Compound (I-3a-5)

MS(FD) m/e: 424(M<sup>+</sup>-Na+1).

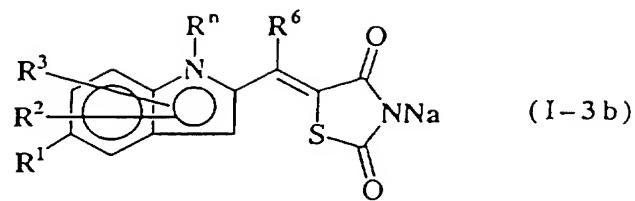
Compound (I-3a-7)

MS(FD) m/e: 410(M<sup>+</sup>-Na+1).

Compound (I-3a-8)

10 MS(FAB<sup>+</sup>) m/e: 387(M<sup>+</sup>-Na+1), 386.

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(R<sup>4</sup>,R<sup>7</sup>=bond , R<sup>6</sup>=H)

Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting materials (I-1b)	Properties (mp °C)
I-3b-9		H	H	H	I-1b-101	Yellow crystals (220-400, decomp.)
I-3b-10		H	H	H	I-1b-102	Yellow crystals (200-400, decomp.)
I-3b-11		H	H	H	I-1b-103	Yellow amorphous (190-210, decomp.)
I-3b-12		H	H	H	I-1b-104	Colorless amorphous (190-220, decomp.)

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Compound (I-3b-9)

MS(FAB<sup>+</sup>) m/e: 395(M<sup>+</sup>+Na), 373.

Compound (I-3b-10)

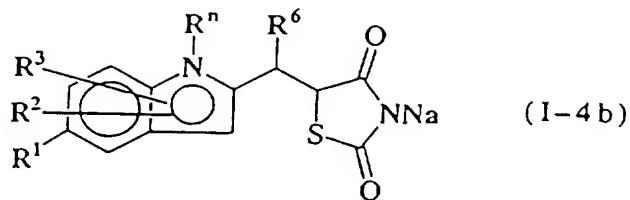
MS(FAB<sup>+</sup>) m/e: 439(M<sup>+</sup>+Na), 417, 416.

5 Compound (I-3b-11)

MS(FAB<sup>+</sup>) m/e: 423(M<sup>+</sup>+Na), 401(M<sup>+</sup>+1), 400(M<sup>+</sup>).

Compound (I-3b-12)

MS(FAB<sup>+</sup>) m/e: 412(M<sup>+</sup>+Na-1), 390(M<sup>+</sup>).



(R<sup>4</sup>,R<sup>7</sup>=bond , R<sup>6</sup>=H)

Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>n</sup>	Starting materials (I-2b)	Properties (mp °C)
I-4b-3		H	H	H	I-2b-5	Pale brown crystals (180-300, decomp.)
I-4b-4		H	H	H	I-2b-8	Pale red amorphous (200-300, decomp.)
I-4b-5		H	H	H	I-2b-9	Yellow amorphous (210-290, decomp.)
I-4b-6		H	H	H	I-2b-10	Colorless amorphous

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Compound (I-4b-3)

MS(FD) m/e:447(M<sup>+</sup>+Na), 425(M<sup>+</sup>+1).

Compound (I-4b-4)

MS(FD) m/e:441(M<sup>+</sup>+Na), 419(M<sup>+</sup>+1).

5 Compound (I-4b-5)

MS(FD) m/e:425(M<sup>+</sup>+Na), 403(M<sup>+</sup>+1).

Compound (I-4b-6)

MS(FAB<sup>+</sup>) m/e:414(M<sup>+</sup>+Na).

TEST EXAMPLE 1: Measurement of hypoglycemic effect

10 KK mouse and KKA<sup>Y</sup> mouse, NIDDM models (male, 6-7 weeks old) (Nakamura, Proc. Jpn. Acad., vol. 38, 348-352, 1962; Iwatsuka et al. Endocrinol. Jpn., vol. 17, 23-35, 1970) were purchased from Nihon Clea. They were allowed free access to high-calories' chow (CMF, Oriental Yeast) 15 and water. Around 40 g-weighted mice were examined.

Blood (20  $\mu$ l) collected from the retro-orbital sinus was diluted in 60 units heparin sodium-solution and was centrifuged in a microfuge. The supernatant was assayed. The glucose concentration was determined by glucose 20 oxidase method (Glucose Analyzer II, Beckman). A group of 3 to 4 mice having a blood glucose value of higher than 200 mg/dl, the blood glucose value of which did not reduce by more than 10% for 24 hours after once oral administration of 0.5% carboxymethyl cellulose (CMC)- 25 saline, were tested.

All test-compounds suspended in 0.5% carboxy-methyl cellulose (CMC)-saline were orally administered in mice.

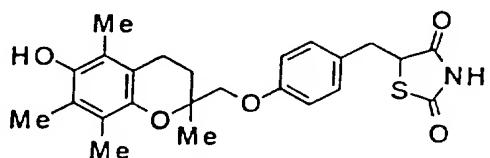
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Before and 24 hours after the administration, blood was collected from the retro-orbital sinus, and a blood glucose value was measured in the above-mentioned manner. The hypoglycemic activity was expressed by the percentage 5 of reducing blood glucose calculated before and 24 hours after the administration.

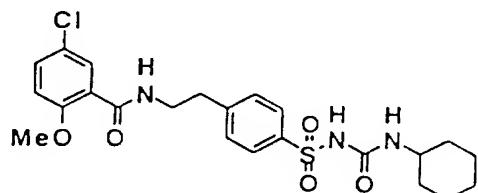
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## KKAY mouse

Compound No.	Dose (mg/kg)	% decrease
I-1a-1	30	17.6
I-1a-3	30	23.4
I-1a-4	30	26.5
I-1b-7	30	14.2
I-1b-13	30	12.7
I-1b-14	30	23.8
I-1b-17	30	17.5
I-1b-18	30	22.6
I-1b-103	30	14.1
I-1b-105	30	19.6
I-2a-1	30	16.0
I-2a-2	30	27.9
I-2a-4	30	15.1
I-2b-6	30	38.0
I-2b-8	30	10.8
I-2b-10	30	20.9
I-2a-19	30	32.2
I-3b-5	30	25.0
I-3b-8	30	18.8
I-3b-9	30	17.5
I-3b-12	30	17.0
I-4a-1	30	28.0
I-4b-5	30	28.4
CS-045	30	-3.0
Glibenclamide	30	-2.5



CS-045



Glibenclamide

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The compounds of the present invention exhibited hypoglycemic activities at substantially higher degree as compared with CS-045 used as controls. Glibenclamide (insulin-releasing agent) did not exhibit hypoglycemic 5 activity in this test.

TEXT EXAMPLE 2: Measurement of hypoglycemic and hypolipidemic effect

db/db mice, NIDDM model (male 6 weeks old), were purchased from Nihon Charles River. They were allowed 10 free access to chow (MF, Oriental Yeast) and water. Around 50 g-weighed mice were examined.

Blood (20  $\mu$ l) collected from the retro-orbital sinus was diluted in 60 units heparin sodium-solution and was centrifuged in a microfuge. The supernatant was assayed. 15 The glucose concentration was determined by glucose oxidase method (Glucose Analyzer II, Beckman). A group of 6 mice were tested.

All test-compounds suspended in 0.5% carboxy-methyl cellulose (CMC)-saline were orally administered in mice 20 once a day for 4 days. Before, 1 day, 2 days, 3 days and 4 days after the administration, blood was collected from the retro-orbital sinus, and a blood glucose value was measured in the above-mentioned manner. The hypoglycemic activity was expressed by the percentage of reducing 25 blood glucose calculated before and 1 day, 2 days, 3 days or 4 days after the administration.

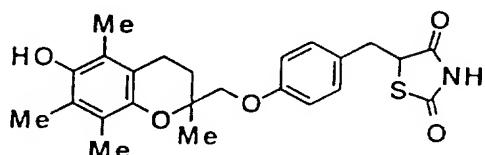
The total cholesterol (TC) amounts in bloods

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collected before drug-administration and 4 days after the drug-administration were measured in accordance with the cholesterol oxidase method and the triglyceride (TG) amounts in theses bloods were measured by the end point 5 method employing glycerol oxidase method. The neutral lipid reducing activity in each blood was expressed by a reducing rate relative to the value before the drug-administration.

The compounds of the present invention exhibited 10 higher hypoglycemic activities and higher neutral lipid reducing activities as compared with CS-045 used as controls.

15	Compound No.	Dose (mg/kg)	% decrease of glucose	% decrease of	
				TC	TG
	I-2b-6	30	10.5	19.5	13.8
20	CS-045	300	17.7	7.1	36.9



CS - 0 4 5

TEST EXAMPLE 3: Measurement of aldose-reductase  
inhibitory activities

Rat kidney AR was prepared as follows; Rat kidney was

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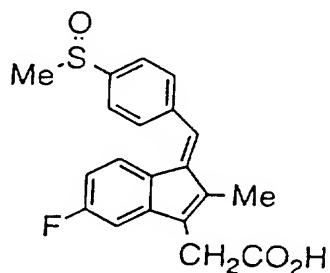
perfused by ice-cold saline to remove blood and then homogenized in a Teflon homogenizer with 3 time volumes of cold 5 mM Tris-HCl buffer (pH 7.4). The homogenate was centrifuged at 45,000  $\times$  g for 40 minutes to remove 5 insoluble materials, and the supernatant fraction was dialyzed overnight against 0.05 M sodium chloride solution. The dialyzed solution was centrifuged again at 11,000  $\times$  g for 20 minutes and the supernatant fraction was used as an aldose reductase sample.

10 Determination of AR and effects of test compounds

AR activity was assayed by the modified method of Inukai et al. (Jpn. J. Pharmacol. 61, 221-227, 1993). The absorbance of NADPH (340 nm), oxidation of the co-factor for AR, was determined by spectrophotometer (UV-15 240, Shimadzu, Kyoto). The assay was carried out in 0.1M sodium phosphate (pH 6.2) containing 0.4M lithium sulfate, 0.15 mM NADPH, the enzyme, various concentrations of test compounds and 10 mM DL-glyceraldehyde. The reference blank contained all of the 20 above ingredients, except for DL-glyceraldehyde. The reaction was started by addition of the substrate (DL-glyceraldehyde). The reaction rate was measured at 30°C for 2 minutes. All test compounds were dissolved in dimethyl sulfoxide (DMSO). The final concentration of 25 DMSO in reaction mixture never exceeded 1%.

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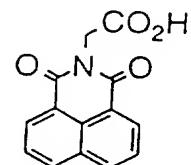
Compound No.	Concentration( $\mu$ M)	% inhibition
I-1a-4	30	100.0
I-1b-14	30	53.4
I-2b-6	100	36.3
I-2b-10	30	23.3
I-3b-5	30	49.6
CS-045	100	0
Sulindac	30	54.0
Quercetin	30	10.8
Alrestatin	100	0



Sulindac



Quercetin



Alrestatin

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The compounds of the present invention exhibited equivalent or stronger aldose-reductase inhibitory activities than sulindac, quercetin or alrestatin used as control. Further, CS-045 exhibited no activities.

5 FORMULATION EXAMPLE 1

Tablets

	The compound of the present invention	1.0 g
	Lactose	5.0 g
	Crystal cellulose powder	8.0 g
10	Corn starch	3.0 g
	Hydroxypropyl cellulose	1.0 g
	CMC-Ca	1.5 g
	Magnesium stearate	0.5 g
<hr/>		
15	Total	20.0 g

The above components were mixed by a usual method and then tabletted to produce 100 tablets each containing 10 mg of the active ingredient.

20 FORMULATION EXAMPLE 2

Capsules

	The compound of the present invention	1.0 g
	Lactose	3.5 g
	Crystal cellulose powder	10.0 g
25	Magnesium stearate	0.5 g
<hr/>		
	Total	15.0 g

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The above components were mixed by a usual method and then packed in No. 4 gelatin capsules to obtain 100 capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 3

5 Soft capsules

	The compound of the present invention	1.00 g
	PEG (polyethylene glycol) 400	3.89 g
	Saturated fatty acid triglyceride	15.00 g
	Peppermint oil	0.01 g
10	Polysorbate 80	0.10 g
<hr/>		
	Total	20.00 g

The above compounds were mixed and packed in No. 3  
15 soft gelatin capsules by a usual method to obtain 100 soft capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 4

Ointment

20	The compound of the present invention	1.0 g (10.0 g)
	Liquid paraffin	10.0 g (10.0 g)
	Cetanol	20.0 g (20.0 g)
	White vaseline	68.4 g (59.4 g)
	Ethylparaben	0.1 g ( 0.1 g)
25	<i>l</i> -menthol	0.5 g ( 0.5 g)
<hr/>		
	Total	100.0 g

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The above components were mixed by a usual method to obtain a 1% (10%) ointment.

FORMULATION EXAMPLE 5

Suppository

5	The compound of the present invention	1.0 g
	Witepsol H15*	46.9 g
	Witepsol W35*	52.0 g
	Polysorbate 80	0.1 g

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10	Total	100.0 g
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\*: Trademark for triglyceride compound

The above components were melt-mixed by a usual method and poured into suppository containers, followed 15 by cooling for solidification to obtain 100 suppositories of 1 g each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 6

Granules

20	The compound of the present invention	1.0 g
	Lactose	6.0 g
	Crystal cellulose powder	6.5 g
	Corn starch	5.0 g
	Hydroxypropyl cellulose	1.0 g
	Magnesium stearate	0.5 g

25

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	Total	20.0 g
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The above components were granulated by a usual method and packaged to obtain 100 packages each containing 200 mg of the granules so that each package contains 10 mg of the active ingredient.

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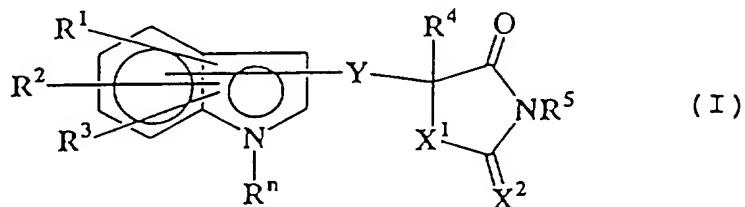
#### INDUSTRIAL APPLICABILITY

Since the compound of the present invention has a hypoglycemic effect and an aldose-reductase inhibitory activity and has less toxicity, it is useful for preventing or treating diabetic complications including 10 diabetic eye diseases (such as diabetic cataract and diabetic retinopathy), diabetic neuropathy, diabetic nephropathy, diabetic gangrene, and the like.

CLAIMS

1. An indole type thiazolidine compound of the following formula (I) and its salt:

5



wherein  $X^1$  is S or O;

10  $X^2$  is S, O or NH;

$Y$  is  $CR^6R^7$  ( $R^6$  is a hydrogen atom, a  $C_1-C_7$  alkyl group or a  $C_3-C_7$  cycloalkyl group, and  $R^7$  is a hydrogen atom, a  $C_1-C_7$  alkyl group or a  $C_3-C_7$  cycloalkyl group, or forms a bond together with  $R^4$ );

15  $R^1$  is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring and is a  $C_1-C_{10}$  alkyl group, a  $C_2-C_{10}$  alkenyl group, a  $C_2-C_{10}$  alkynyl group, a  $C_1-C_{10}$  alkoxy group, a  $C_2-C_{10}$  alkenyloxy group, a  $C_1-C_{10}$  alkylthio group, a  $C_1-C_{10}$  monoalkylamino group or a di-  
20  $C_1-C_{10}$  alkylamino group (each of said  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{10}$  alkynyl,  $C_1-C_{10}$  alkoxy,  $C_2-C_{10}$  alkenyloxy,  $C_1-C_{10}$  alkylthio,  $C_1-C_{10}$  monoalkylamino and di- $C_1-C_{10}$  alkylamino groups may be substituted with a hydroxyl group or a  $C_1-C_7$  alkyl group), or

25  $-W_k-V_\ell-Z$  ( $Z$  is a  $C_3-C_{10}$  cycloalkyl group, a  $C_3-C_7$  cycloalkenyl group, a  $C_6-C_{14}$  aromatic group, a  $C_1-C_{12}$  heterocyclic aromatic group (said heterocyclic aromatic

group may contain at most 5 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring), or a C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic group (said

5 heterocycloaliphatic group may contain at most 3 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring) (each of said C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, C<sub>6</sub>-C<sub>14</sub> aromatic, C<sub>1</sub>-C<sub>12</sub>

10 heterocyclic aromatic and C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be

15 substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl

20 group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl,

25 thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub>,

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cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a

5 thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group),

W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated

10 hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups, and each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two

15 W's may be the same or different), or

R<sup>1</sup> may be a hydrogen atom when Y is bonded to the 4-, 5-, 6- or 7-position of an indole ring;

each of R<sup>2</sup> and R<sup>3</sup> is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring, and is

20 independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group (said C<sub>1</sub>-C<sub>7</sub> alkyl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl groups may be substituted with a hydroxyl group), a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a benzyloxy group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group, a

25 pyrimidinyl group, a pyridazinyl group, a furanyl group, a thieryl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, a pyranyl group, a quinolyl group, a

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benzoxazolyl group, a benzothiazolyl group or a benzimidazolyl group (each of said phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl,

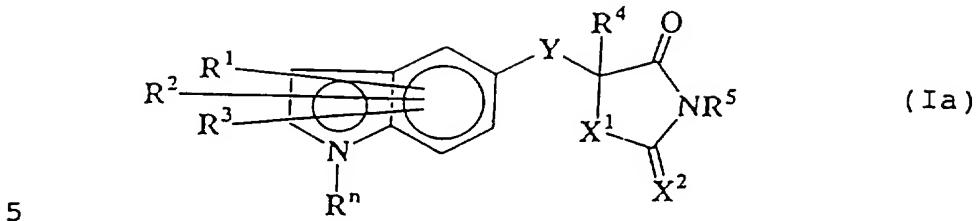
5 quinolyl, benzoxazolyl, benzothiazolyl and benzimidazolyl groups may be substituted with at most 5 members selected from the group consisting of a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group and a halogen atom), a hydroxyl group or a halogen atom;

10 R<sup>4</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>7</sub> alkyl group, or forms a bond together with R<sup>7</sup>;

R<sup>5</sup> is a hydrogen atom or a carboxymethyl group; and

15 R<sup>n</sup> is a substituent at the 1-position of an indole ring, and is a hydrogen atom, C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>4</sub> alkoxyethyl group, an aryloxyethyl group, a C<sub>1</sub>-C<sub>4</sub> alkylaminomethyl group, a substituted acetamidemethyl group, a substituted thiomethyl group, a carboxyl group, a C<sub>1</sub>-C<sub>7</sub> acyl group, an arylcarbonyl group, a C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl group, an 20 aryloxy carbonyl group, a C<sub>1</sub>-C<sub>4</sub> alkylaminocarbonyl group, an arylaminocarbonyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkoxyalkyloxy group, a trialkylsilyl group, a trialkylarylsilyl group, an alkylsulfonyl group or an arylsulfonyl group.

25 2. The indole type thiazolidine compound and its salt according to Claim 1, wherein the compound of the formula (I) is represented by the following formula (Ia):



wherein R<sup>1</sup> is a substituent at the 2-, 3-, 4-, 6- or 7-position of an indole ring and is a hydrogen atom, a C<sub>1</sub>-C<sub>10</sub> alkyl group, a C<sub>2</sub>-C<sub>10</sub> alkenyl group, a C<sub>2</sub>-C<sub>10</sub> alkynyl group, a C<sub>1</sub>-C<sub>10</sub> alkoxy group, a C<sub>2</sub>-C<sub>10</sub> alkenyloxy group, a 10 C<sub>1</sub>-C<sub>10</sub> alkylthio group, a C<sub>1</sub>-C<sub>10</sub> monoalkylamino group or a di-C<sub>1</sub>-C<sub>10</sub> alkylamino group (each of said C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, C<sub>2</sub>-C<sub>10</sub> alkenyloxy, C<sub>1</sub>-C<sub>10</sub> alkylthio, C<sub>1</sub>-C<sub>10</sub> monoalkylamino and di-C<sub>1</sub>-C<sub>10</sub> alkylamino groups may be substituted with a 15 hydroxyl group or a C<sub>1</sub>-C<sub>6</sub> alkyl group), or

-W<sub>k</sub>-V<sub>l</sub>-Z (among groups of Z as defined for the formula (I), said C<sub>3</sub>-C<sub>10</sub> cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, 20 bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl, said C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C<sub>6</sub>-C<sub>14</sub> aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C<sub>1</sub>-C<sub>12</sub> heterocyclic aromatic group is furyl, thienyl, 25 pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl,

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oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl,  
pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl,  
pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl,  
tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl,  
5 benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl,  
benzothiazolyl, benzopyrazolyl, benzimidazolyl,  
benzotriazolyl, benzopyranyl, indolizinyl, purinyl,  
phthalazinyl, oxophthalazinyl, naphthyridinyl,  
quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl,  
10 benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl,  
benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl,  
pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-  
b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-  
benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl,  
15 carbazolyl, acridinyl, phenazinyl, phenothiazinyl,  
phenoxazinyl, or thianthrenyl, and said C<sub>1</sub>-C<sub>6</sub>  
heterocycloaliphatic group is piperidyl, pyrrolidinyl,  
imidazolidinyl, pyrazolidinyl, morpholinyl, or  
tetrahydrofuranyl, (each of said C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub>  
20 cycloalkenyl, C<sub>6</sub>-C<sub>14</sub> aromatic, C<sub>1</sub>-C<sub>12</sub> heterocyclic  
aromatic and C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic groups may have  
at most 5 substituents selected from the group consisting  
of a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub>  
cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl,  
25 cycloalkyl and cycloalkenyl groups may be substituted  
with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy  
group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a halogen atom, a

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trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted 5 with at most 5 substituents selected from the group 10 consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3- 15 tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group),

20 W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups, and each of k and ℓ is 0 or 1),

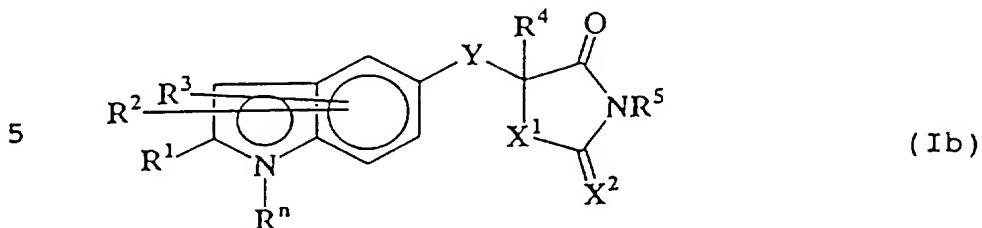
-V-W-Z (V, W and Z are as defined above), or

25 -W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

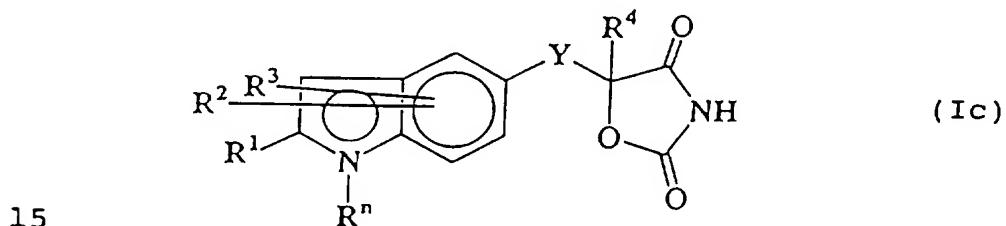
3. The indole type thiazolidine compound and its salt

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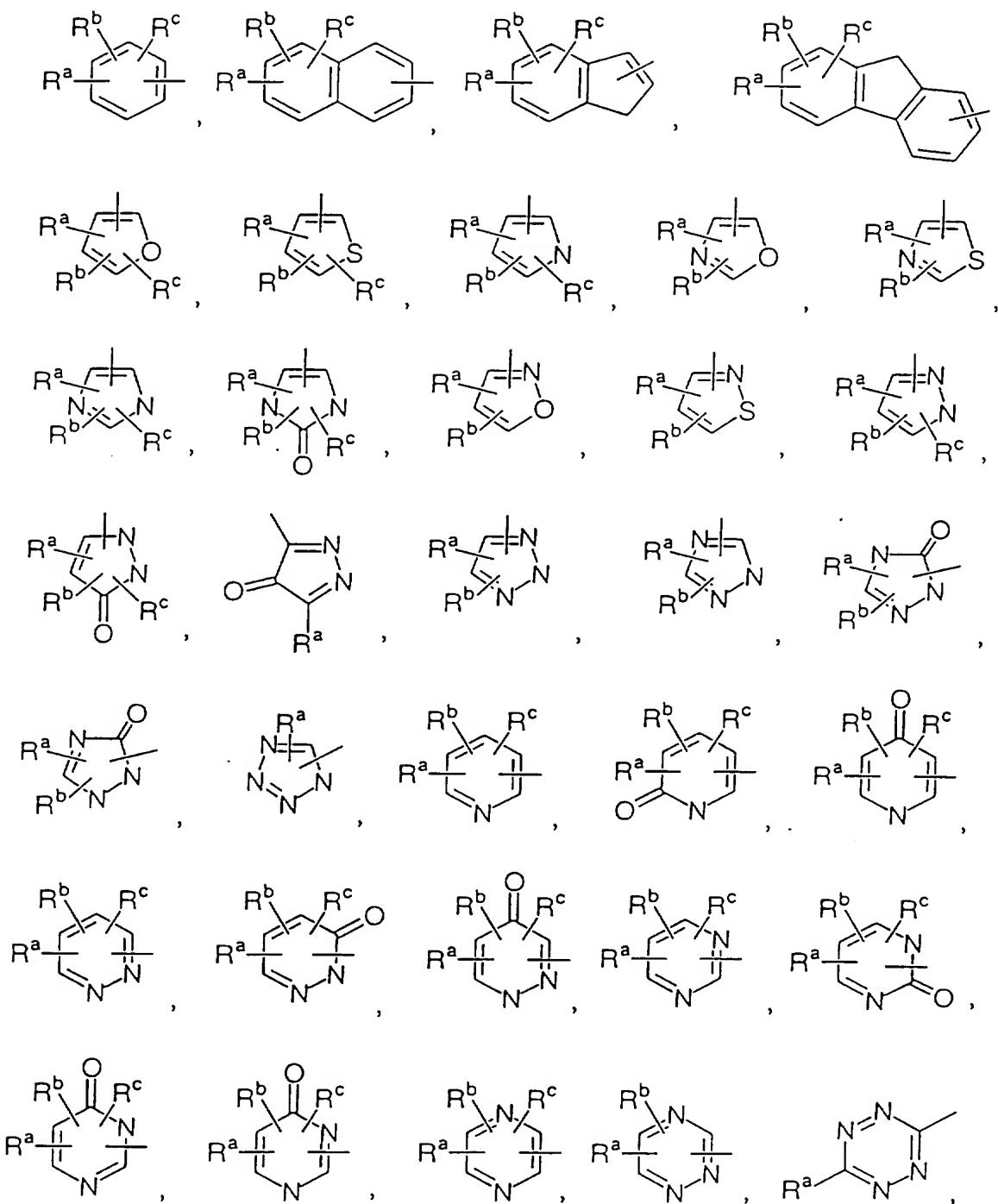
according to Claim 2, wherein the compound of the formula (Ia) is represented by the formula (Ib):

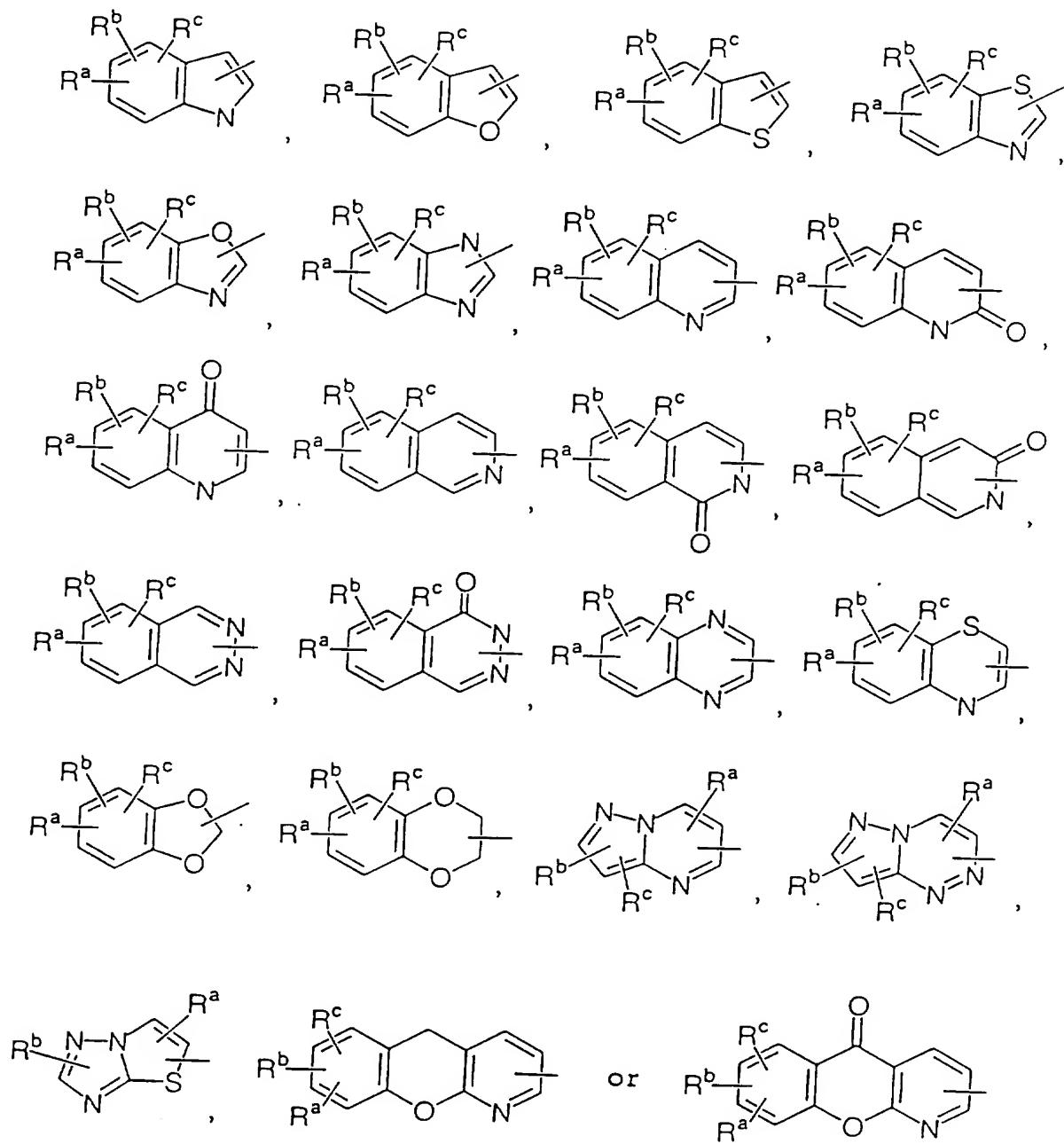


4. The indole type thiazolidine compound and its salt according to Claim 3, wherein the compound of the formula 10 (Ib) is represented by the formula (Ic):



wherein R<sup>1</sup> is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group), W is a divalent C<sub>1</sub>-C<sub>6</sub> 20 saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups, when two W's are present, such W's may be the same or different, and Z is





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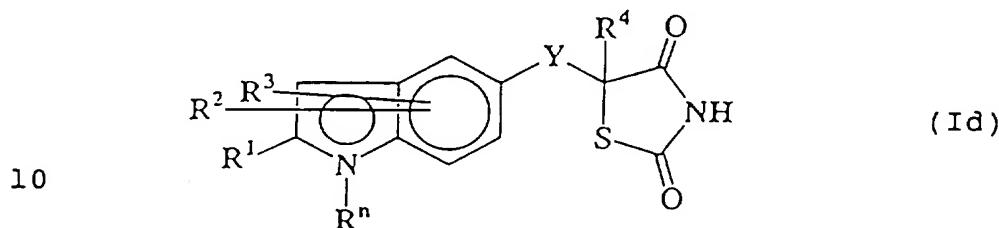
wherein each of R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group);

R<sup>2</sup> or R<sup>3</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a

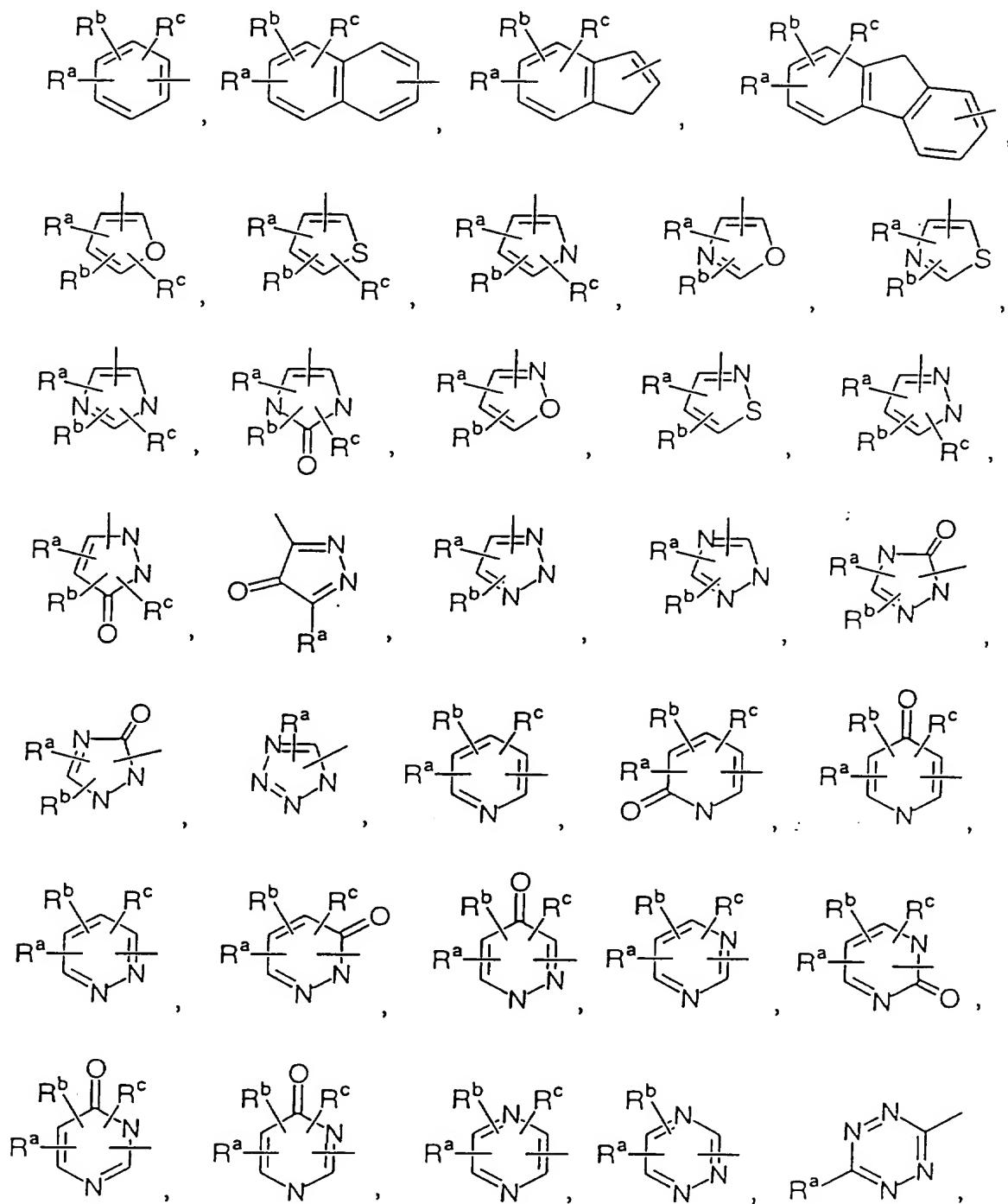
- 247 -

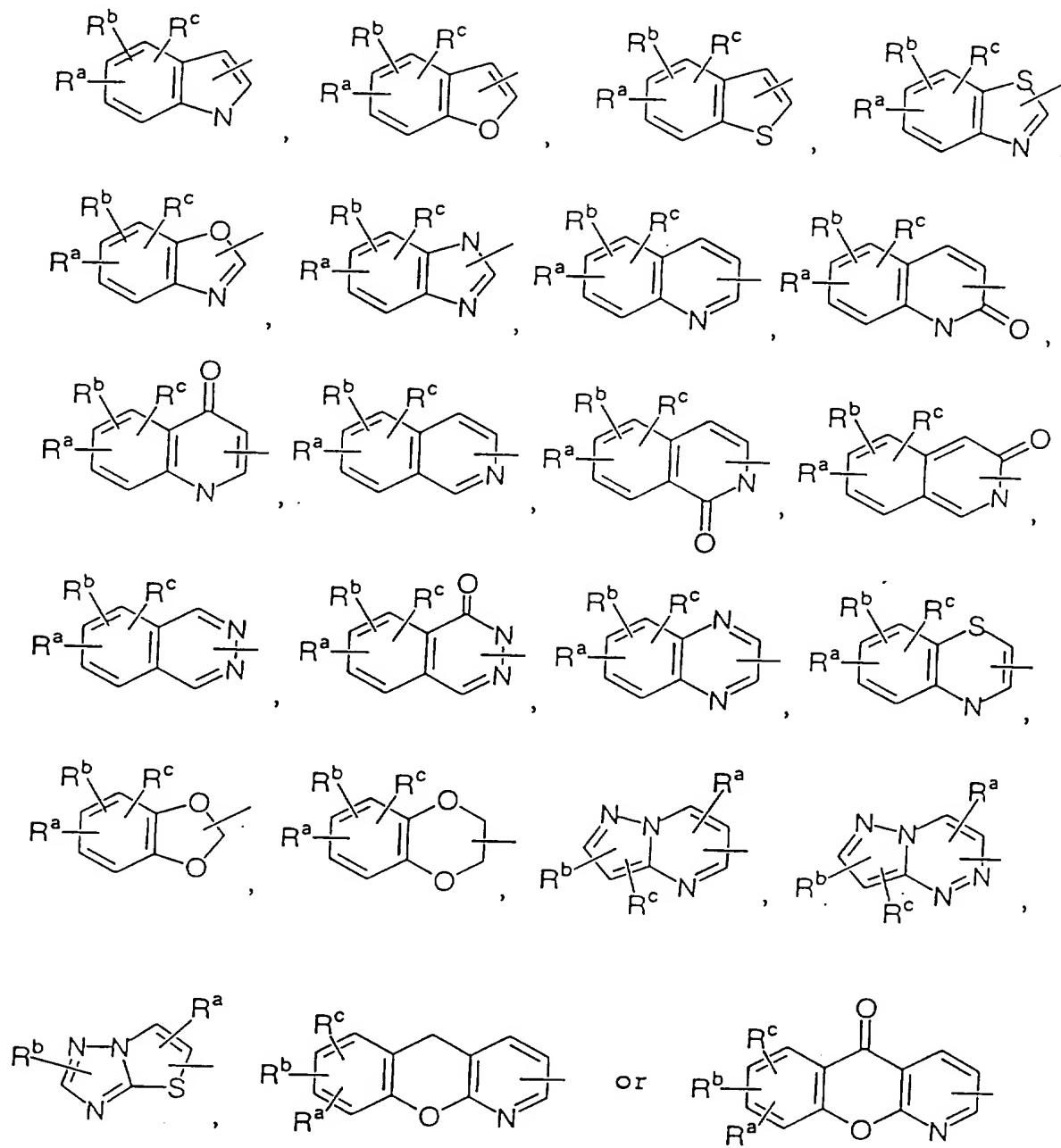
$C_3-C_6$  cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and  $R^5$  is a hydrogen atom.

5. The indole type thiazolidine compound and its salt  
5 according to Claim 3, wherein the compound of the formula  
(Ib) is represented by the formula (Id):



wherein  $R^1$  is a substituent at the 2-position of an indole ring, and is  $-W-Z$ ,  $-V-Z$ ,  $-W-V-Z$ ,  $-V-W-Z$  or  $-W-V-W-Z$  ( $V$  is  $O$ ,  $S$ ,  $SO$ ,  $SO_2$  or  $NR^8$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group),  $W$  is a divalent  $C_1-C_6$  saturated or  $C_2-C_6$  unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and  $C_1-C_7$  alkyl groups, when two  $W$ 's are present, such  $W$ 's may be the same or different, and  $Z$  is





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wherein each of R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonyl amide group, a 5 carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of 10 said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group 15 consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a 20 hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> 25 alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group);

R<sup>2</sup> or R<sup>3</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a

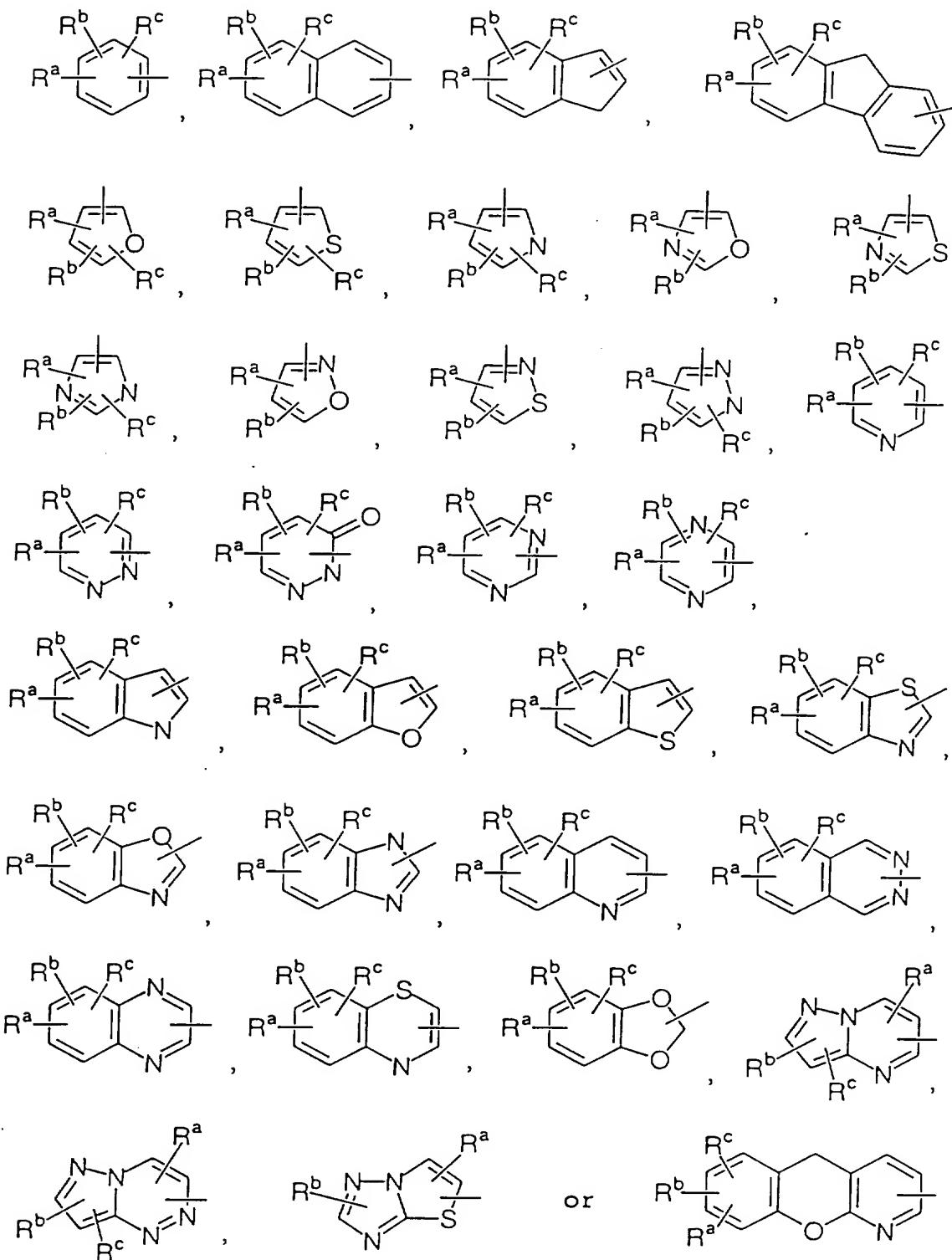
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$C_3-C_6$  cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and  $R^5$  is a hydrogen atom.

6. The indole type thiazolidine compound and its salt  
5 according to Claim 5, wherein Y is  $CR^6R^7$  ( $R^6$  is a hydrogen atom or a methyl group, and  $R^7$  is a hydrogen atom, or forms a bond together with  $R^4$ );

$R^1$  is a substituent at the 2-position of an indole ring, and is  $-W-Z$ ,  $-V-Z$ ,  $-W-V-Z$ ,  $-V-W-Z$  or  $-W-V-W-Z$  (V is 10 O, S, SO,  $SO_2$  or  $NR^8$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group), W is a divalent  $C_1-C_6$  saturated or  $C_2-C_6$  unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and  $C_1-C_7$  alkyl groups (provided that the first carbon atom bonded to N is not 15 substituted with a hydroxyl group and the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group), when two W's are present, such W's may be the same or different, and Z is

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wherein each  $R^a$  and  $R^b$  is independently a hydrogen atom, a  $C_1$ - $C_7$  alkyl group, a  $C_3$ - $C_7$  cycloalkyl group, a  $C_3$ - $C_7$  cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a  $C_1$ - $C_7$  alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonyl amide group, a carboxyl group, a  $C_1$ - $C_3$  alkoxy carbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri- $C_1$ - $C_7$ -alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a  $C_1$ - $C_7$  alkyl group, a  $C_3$ - $C_7$  cycloalkyl group, a  $C_1$ - $C_3$  alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and  $R^c$  is a hydrogen atom, a  $C_1$ - $C_7$  alkyl group, a  $C_3$ - $C_7$  cycloalkyl group or a hydroxymethyl group);

$R^4$  is a hydrogen atom or a methyl group, or forms a bond together with  $R^7$ ; and

$R^n$  is a substituent at the 1-position of an indole

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ring, and is a hydrogen atom, a C<sub>1</sub>-C<sub>3</sub> alkyl group, a cyclopropyl group, a C<sub>1</sub>-C<sub>2</sub> alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group and a 5 trialkylsilyl group.

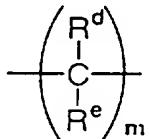
7. The indole type thiazolidine compound and its salt according to Claim 6, wherein:

R<sup>1</sup> is -W-Z, wherein W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be 10 substituted with at most 2 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups.

8. The indole type thiazolidine compound and its salt according to Claim 7, wherein:

R<sup>1</sup> is -W-Z, wherein W is

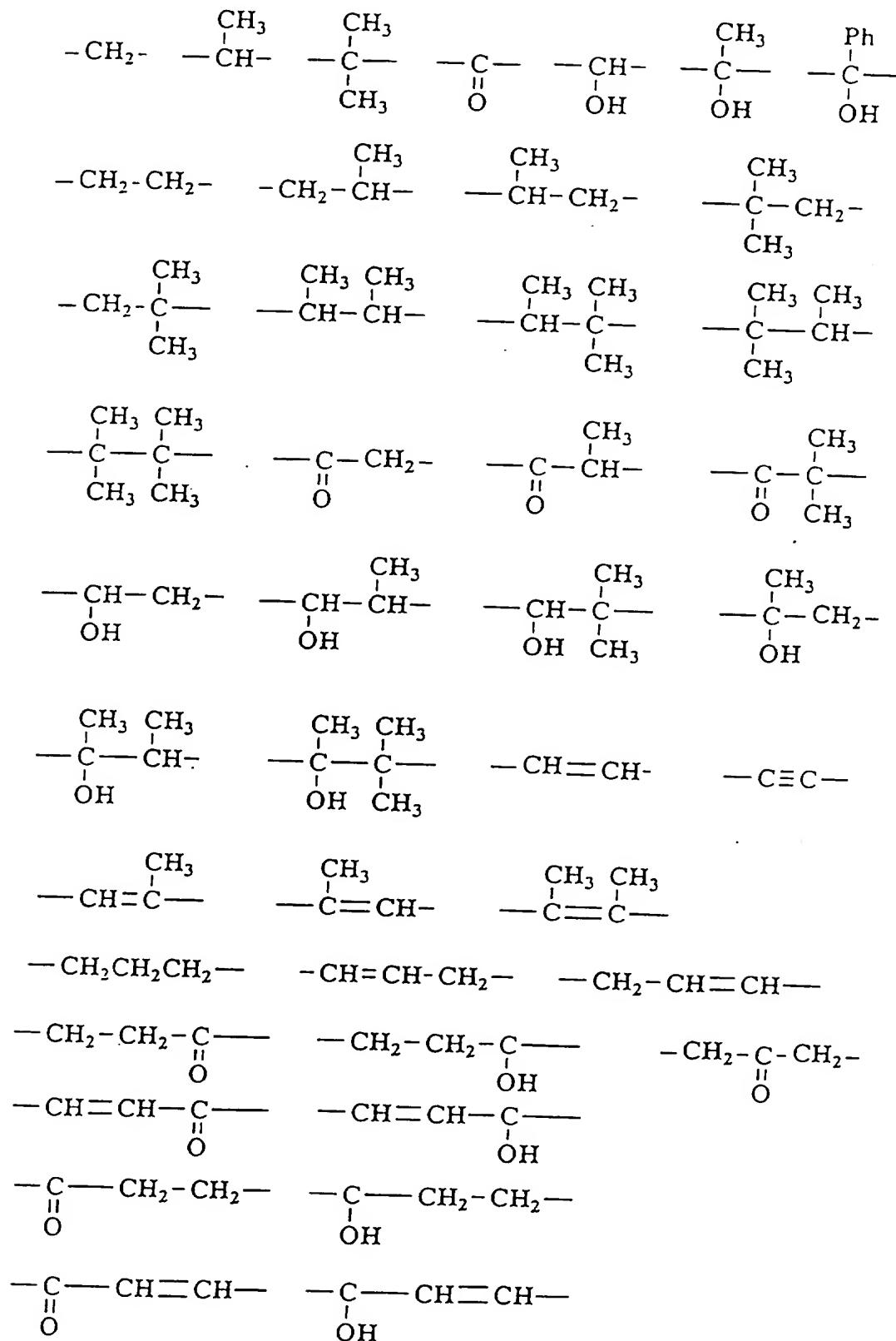
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wherein m is from 1 to 5, and each of R<sup>d</sup> and R<sup>e</sup> is independently a hydrogen atom, a methyl group or a 20 hydroxyl group, or R<sup>d</sup> and R<sup>e</sup> together form an oxo group, or adjacent R<sup>d</sup>'s together form a double bond, or adjacent R<sup>d</sup>'s and R<sup>e</sup>'s together form a triple bond.

9. The indole type thiazolidine compound and its salt according to Claim 8, wherein:

25 R<sup>1</sup> is -W-Z, wherein W is



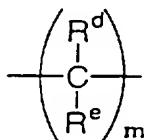
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10. The indole type thiazolidine compound and its salt according to Claim 6, wherein:

R<sup>1</sup> is -V-Z, wherein V is S, SO or SO<sub>2</sub>.

11. The indole type thiazolidine compound and its salt 5 according to Claim 6, wherein:

R<sup>1</sup> is -W-V-Z, wherein W is



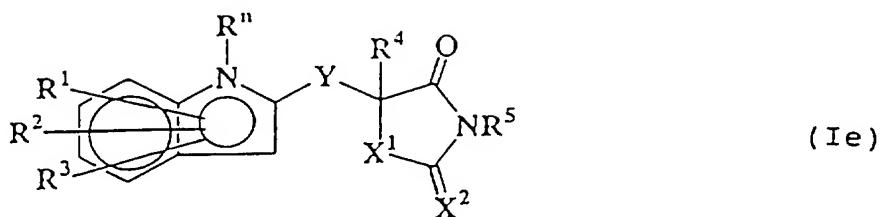
10 wherein m is from 1 to 5, and each of R<sup>d</sup> and R<sup>e</sup> is independently a hydrogen atom, a methyl group or a hydroxyl group, or R<sup>d</sup> and R<sup>e</sup> together form an oxo group, or adjacent R<sup>d</sup>'s together form a double bond, or adjacent R<sup>d</sup>'s and R<sup>e</sup>'s together form a triple bond (provided that 15 R<sup>d</sup> and R<sup>e</sup> on the first carbon atom adjacent to N are not hydroxyl groups and also provided that R<sup>d</sup> and R<sup>e</sup> on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group),

20 V is NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group).

12. The indole type thiazolidine compound and its salt according to Claim 11, wherein:

R<sup>1</sup> is -W-V-Z, wherein -W-V- is -CO-NR<sup>8</sup>- (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group).

25 13. The indole type thiazolidine compound and its salt according to Claim 1, wherein the compound of the formula (I) is represented by the following formula (Ie):



5 wherein  $R^1$  is a substituent at the 3-, 4-, 5-, 6- or 7-position of an indole ring, and is a  $C_1-C_{10}$  alkyl group, a  $C_2-C_{10}$  alkenyl group, a  $C_2-C_{10}$  alkynyl group, a  $C_1-C_{10}$  alkoxy group, a  $C_2-C_{10}$  alkenyloxy group, a  $C_1-C_{10}$  alkylthio group, a  $C_1-C_{10}$  monoalkylamino group or a di- $C_1-C_{10}$  alkylamino group (each of said  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{10}$  alkynyl,  $C_1-C_{10}$  alkoxy,  $C_2-C_{10}$  alkenyloxy,  $C_1-C_{10}$  alkylthio,  $C_1-C_{10}$  monoalkylamino and di- $C_1-C_{10}$  alkylamino groups may be substituted with a hydroxyl group or a  $C_1-C_7$  alkyl group), or

10  $-W_k-V_\ell-Z$  (among groups of  $Z$  as defined for the formula (I), said  $C_3-C_{10}$  cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl,

15 said  $C_3-C_7$  cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said  $C_6-C_{14}$  aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said  $C_1-C_{12}$  heterocyclic aromatic group is furyl, thieryl,

20 pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl, oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl,

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pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl,  
pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl,  
tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl,  
benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl,  
5 benzothiazolyl, benzopyrazolyl, benzimidazolyl,  
benzotriazolyl, benzopyranyl, indolizinyl, purinyl,  
phthalazinyl, oxophthalazinyl, naphthyridinyl,  
quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl,  
benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl,  
10 benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl,  
pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-  
b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-  
benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl,  
carbazolyl, acridinyl, phenazinyl, phenothiazinyl,  
15 phenoxazinyl, or thianthrenyl, and said C<sub>1</sub>-C<sub>6</sub>  
heterocycloaliphatic group is piperidyl, pyrrolidinyl,  
imidazolidinyl, pyrazolidinyl, morpholinyl, or  
tetrahydrofuranyl, (each of said C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub>,  
cycloalkenyl, C<sub>6</sub>-C<sub>14</sub> aromatic, C<sub>1</sub>-C<sub>12</sub> heterocyclic  
20 aromatic and C<sub>1</sub>-C<sub>6</sub> heterocycloaliphatic groups may have  
at most 5 substituents selected from the group consisting  
of a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub>  
cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl,  
cycloalkyl and cycloalkenyl groups may be substituted  
25 with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy  
group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a halogen atom, a  
trifluoromethyl group, a nitro group, an amino group, a

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methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a 15 thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO<sub>2</sub> or NR<sup>8</sup> (R<sup>8</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>3</sub> alkyl group),

W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups, and each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two

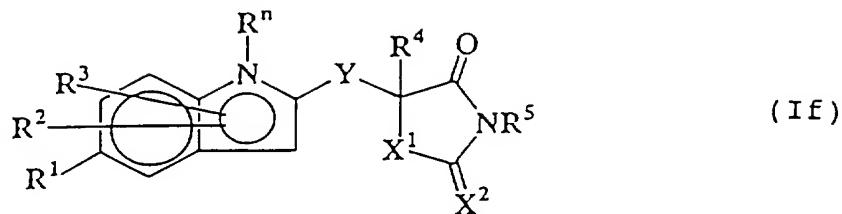
25 W's may be the same or different).

14. The indole type thiazolidine compound and its salt according to Claim 13, wherein the compound of the

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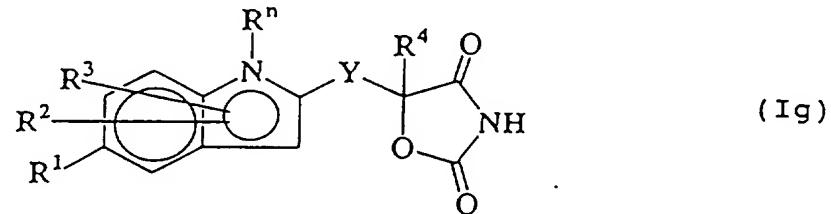
formula (Ie) is represented by the formula (If):

5



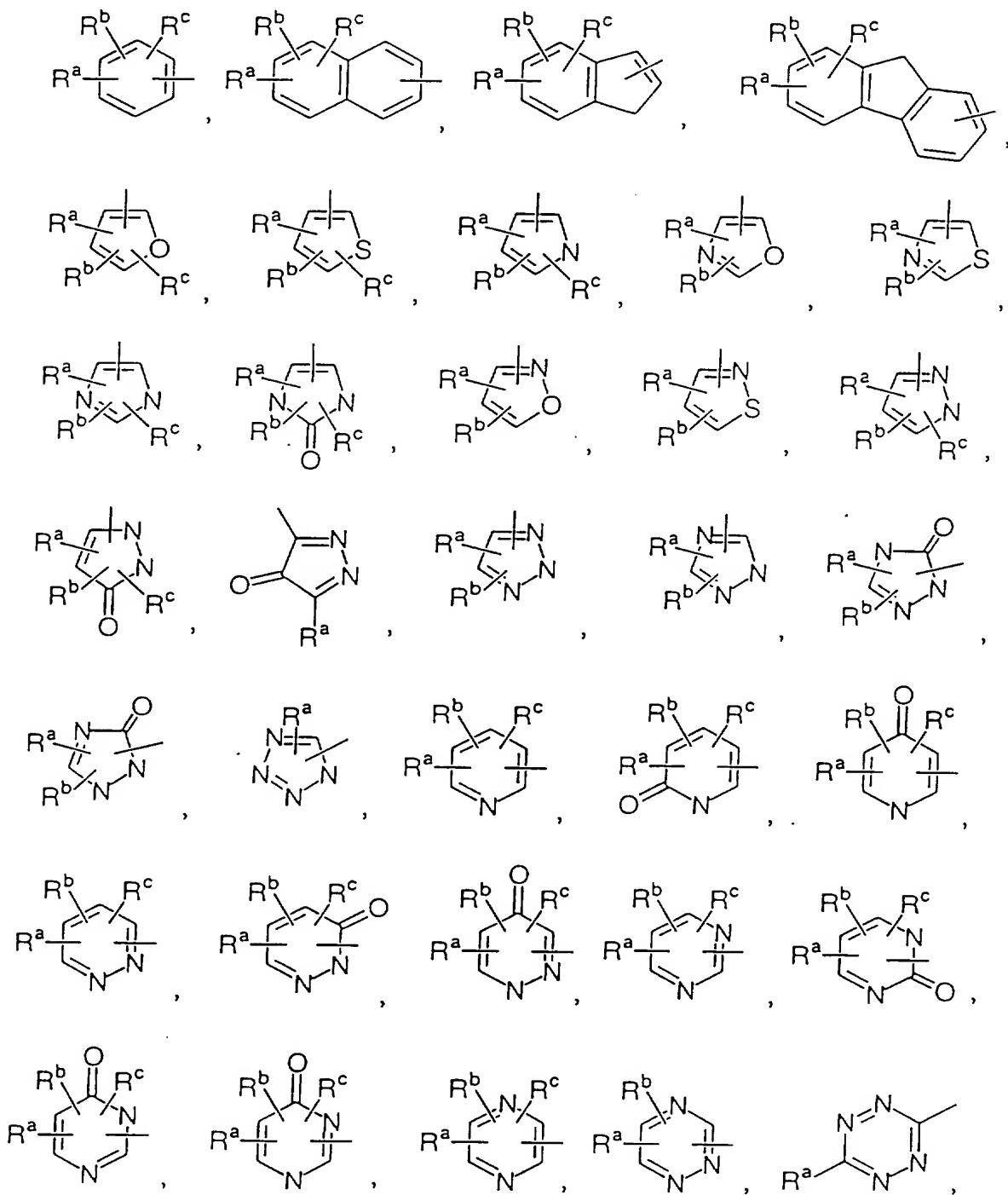
(If)

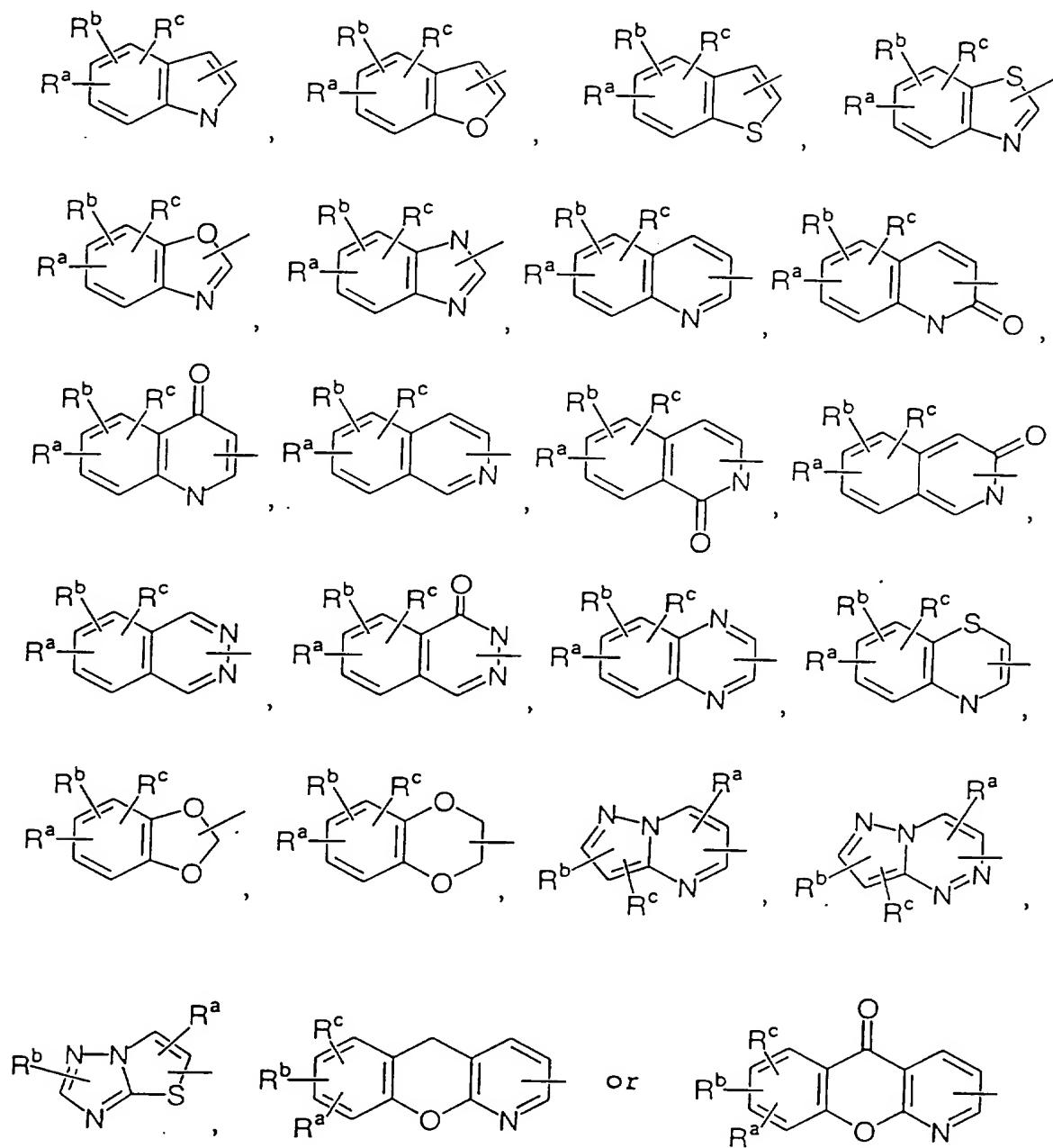
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15 wherein  $\text{R}^1$  is a substituent at the 5-position of an indole ring, and is  $-\text{W}-\text{Z}$ ,  $-\text{V}-\text{Z}$ ,  $-\text{W}-\text{V}-\text{Z}$ ,  $-\text{V}-\text{W}-\text{Z}$  or  $-\text{W}-\text{V}-\text{W}-\text{Z}$  ( $\text{V}$  is  $\text{O}$ ,  $\text{S}$ ,  $\text{SO}$ ,  $\text{SO}_2$  or  $\text{NR}^8$  ( $\text{R}^8$  is a hydrogen atom or a  $\text{C}_1\text{-C}_3$  alkyl group),  $\text{W}$  is a divalent  $\text{C}_1\text{-C}_6$  saturated or  $\text{C}_2\text{-C}_6$  unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and  $\text{C}_1\text{-C}_7$  alkyl groups, when two  $\text{W}$ 's are present, such  $\text{W}$ 's may be the same or different, and  $\text{Z}$  is

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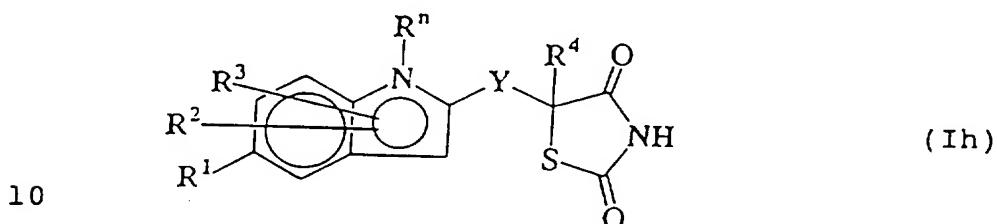
wherein each of R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a 5 carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of 10 said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group 15 consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a 20 hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> 25 alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group);

R<sup>2</sup> or R<sup>3</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a

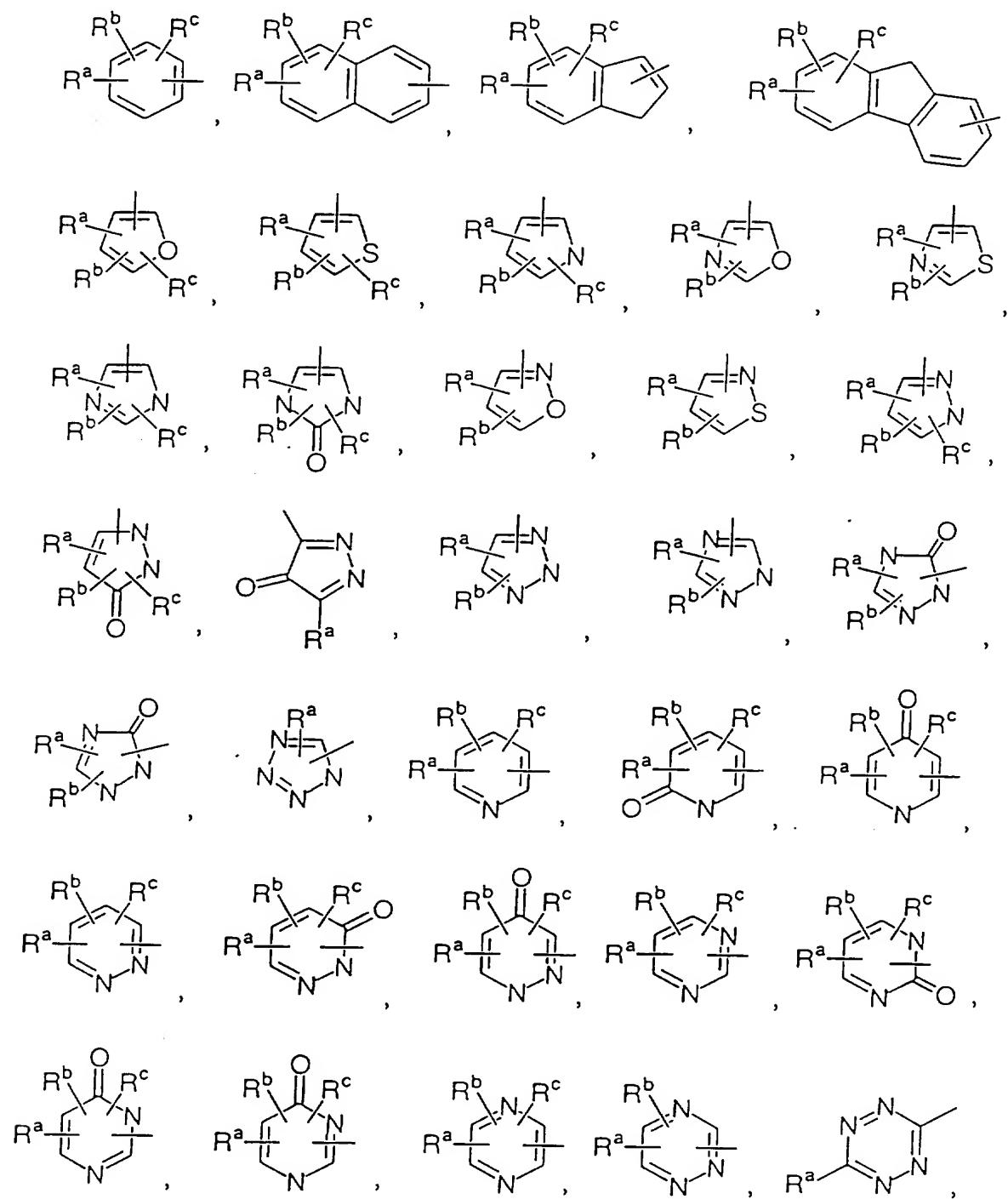
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$C_3-C_6$  cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and  $R^5$  is a hydrogen atom.

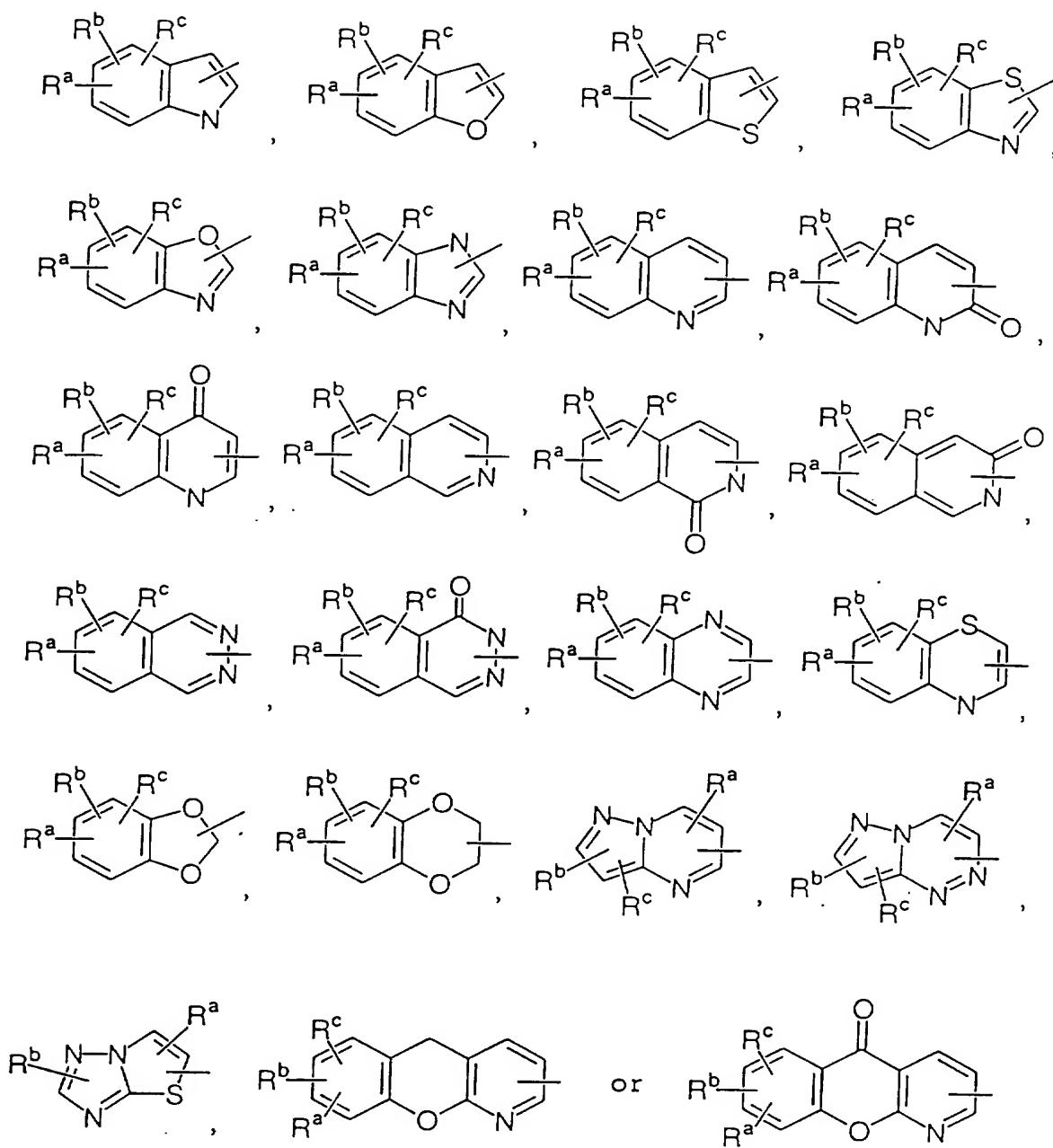
16. The indole type thiazolidine compound and its salt  
5 according to Claim 14, wherein the compound of the formula (If) is represented by the formula (Ih):



wherein  $R^1$  is a substituent at the 5-position of an indole ring, and is  $-W-Z$ ,  $-V-Z$ ,  $-W-V-Z$ ,  $-V-W-Z$  or  $-W-V-W-Z$  ( $V$  is O, S,  $SO$ ,  $SO_2$  or  $NR^8$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group)),  $W$  is a divalent  $C_1-C_6$  saturated or  $C_2-C_6$  unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and  $C_1-C_7$  alkyl groups, when two  $W$ 's are present, such  $W$ 's may be the same or different, and  $Z$  is



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wherein each of R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a C<sub>1</sub>-C<sub>7</sub> alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyloxy group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a C<sub>1</sub>-C<sub>3</sub> alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group;

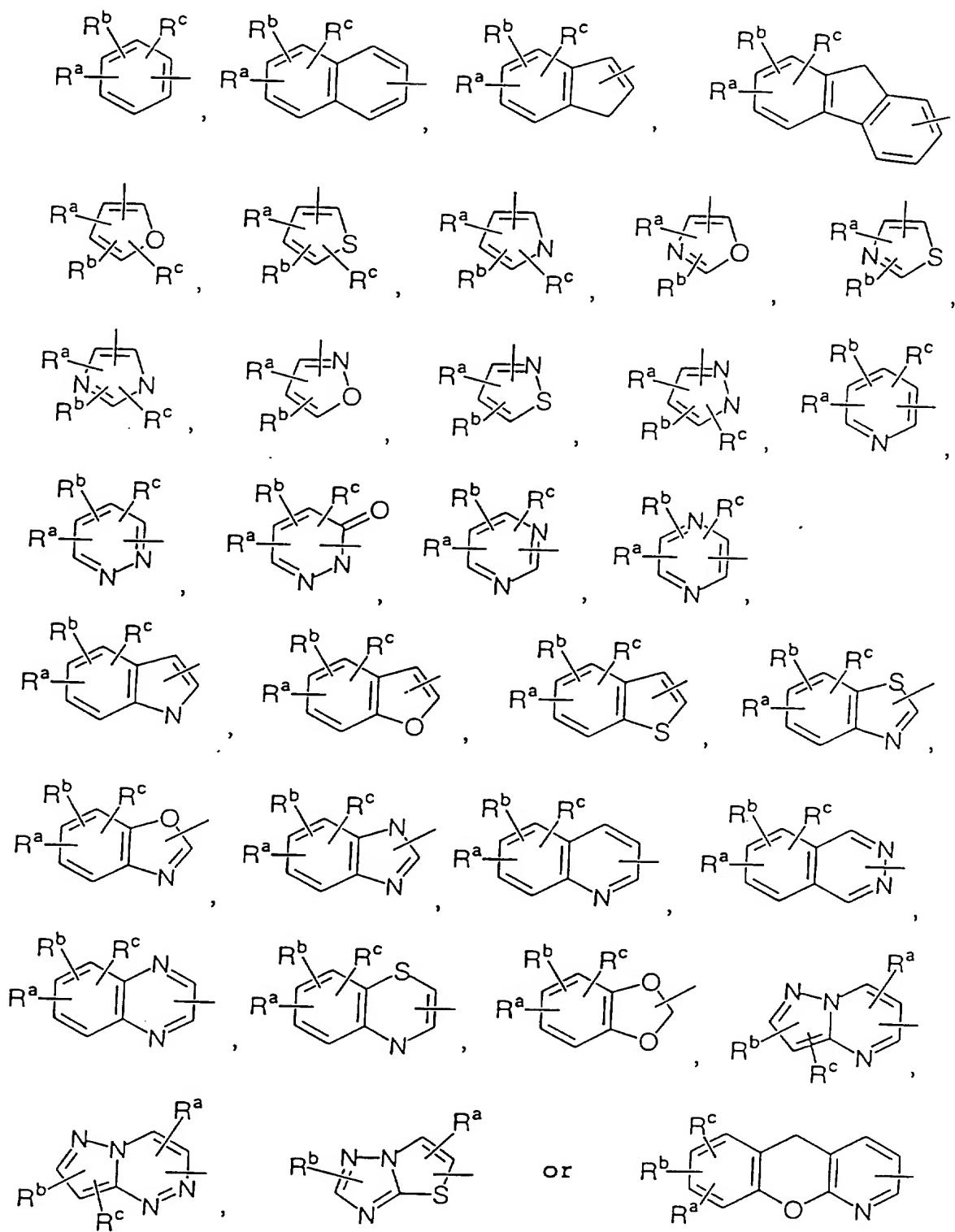
R<sup>2</sup> or R<sup>3</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a

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$C_3-C_6$  cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and  $R^5$  is a hydrogen atom.

17. The indole type thiazolidine compound and its salt  
5 according to Claim 16, wherein Y is  $CR^6R^7$  ( $R^6$  is a hydrogen atom or a methyl group, and  $R^7$  is a hydrogen atom, or forms a bond together with  $R^4$ );

$R^1$  is a substituent at the 5-position of an indole ring, and is  $-W-Z$ ,  $-V-Z$ ,  $-W-V-Z$ ,  $-V-W-Z$  or  $-W-V-W-Z$  (V is 10 O, S,  $SO_2$  or  $NR^8$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group), W is a divalent  $C_1-C_6$  saturated or  $C_2-C_6$  unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and  $C_1-C_7$  alkyl groups (provided that the first carbon atom bonded to N is not 15 substituted with a hydroxyl group and the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group), when two W's are present, such W's may be the same or different, and Z is



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wherein each R<sup>a</sup> and R<sup>b</sup> is independently a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C<sub>1</sub>-C<sub>7</sub> alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonyl group, a carboxyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri-C<sub>1</sub>-C<sub>7</sub>-alkylsilyl group, a phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R<sup>c</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>7</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group or a hydroxymethyl group);

R<sup>4</sup> is a hydrogen atom or a methyl group, or forms a bond together with R<sup>7</sup>; and

R<sup>n</sup> is a substituent at the 1-position of an indole

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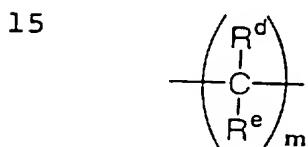
ring, and is a hydrogen atom, a C<sub>1</sub>-C<sub>3</sub> alkyl group, a cyclopropyl group, a C<sub>1</sub>-C<sub>2</sub> alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C<sub>1</sub>-C<sub>3</sub> alkoxy group and a 5 trialkylsilyl group.

18. The indole type thiazolidine compound and its salt according to Claim 17, wherein:

R<sup>1</sup> is -W-Z, wherein W is a divalent C<sub>1</sub>-C<sub>6</sub> saturated or C<sub>2</sub>-C<sub>6</sub> unsaturated hydrocarbon group which may be 10 substituted with at most 2 of hydroxyl, oxo and C<sub>1</sub>-C<sub>7</sub> alkyl groups.

19. The indole type thiazolidine compound and its salt according to Claim 18, wherein:

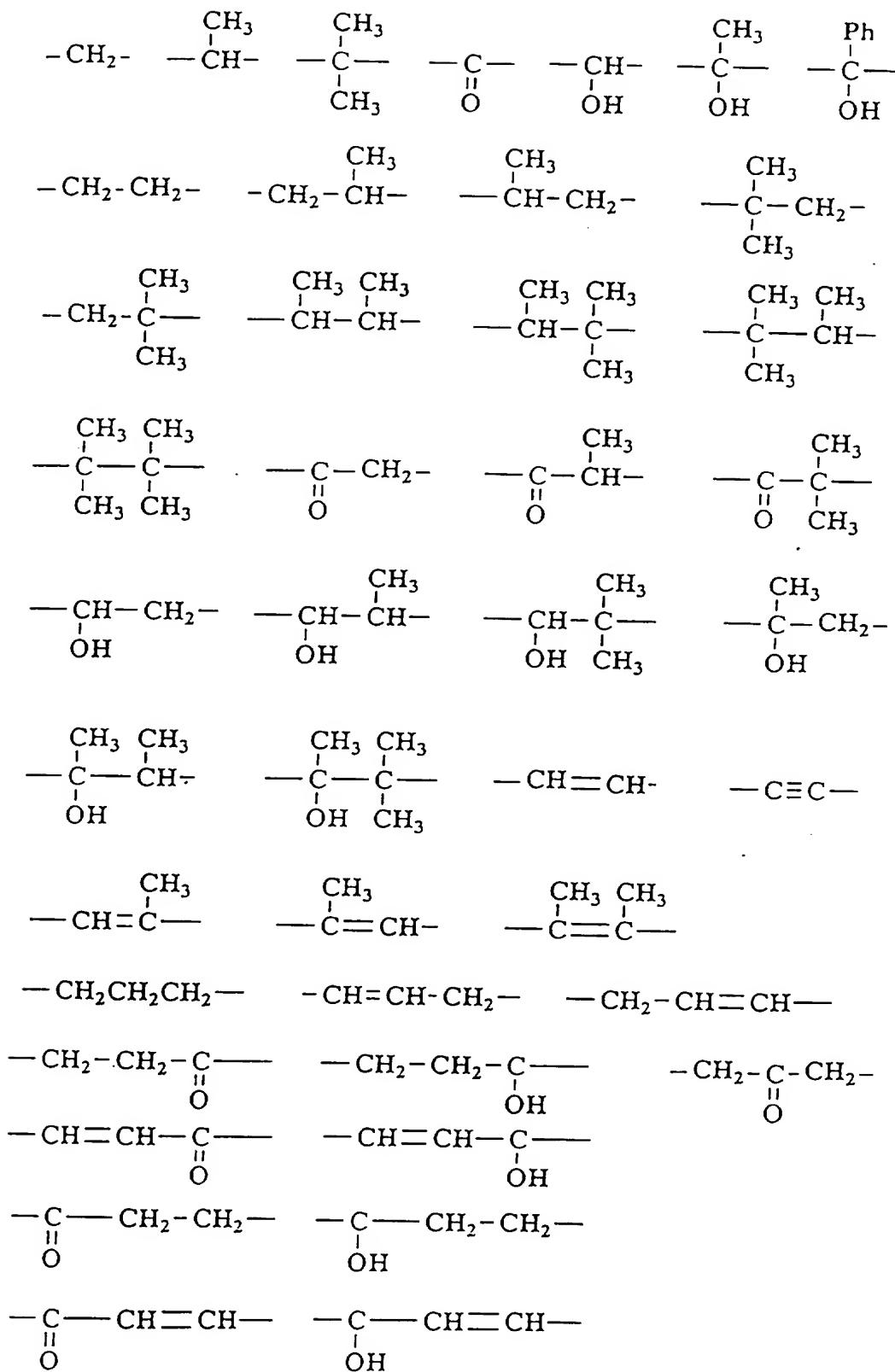
R<sup>1</sup> is -W-Z, wherein W is



wherein m is from 1 to 5, and each of R<sup>d</sup> and R<sup>e</sup> is independently a hydrogen atom, a methyl group or a 20 hydroxyl group, or R<sup>d</sup> and R<sup>e</sup> together form an oxo group, or adjacent R<sup>d</sup>'s together form a double bond, or adjacent R<sup>d</sup>'s and R<sup>e</sup>'s together form a triple bond.

20. The indole type thiazolidine compound and its salt according to Claim 19, wherein:

25 R<sup>1</sup> is -W-Z, wherein W is



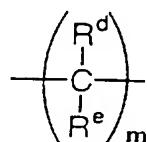
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21. The indole type thiazolidine compound and its salt according to Claim 17, wherein:

$R^1$  is  $-V-Z$ , wherein  $V$  is  $S$ ,  $SO$  or  $SO_2$ .

22. The indole type thiazolidine compound and its salt according to Claim 17, wherein:

$R^1$  is  $-W-V-Z$ , wherein  $W$  is



wherein  $m$  is from 1 to 5, and each of  $R^d$  and  $R^e$  is independently a hydrogen atom, a methyl group or a hydroxyl group, or  $R^d$  and  $R^e$  together form an oxo group, or adjacent  $R^d$ 's together form a double bond, or adjacent  $R^d$ 's and  $R^e$ 's together form a triple bond (provided that  $R^d$  and  $R^e$  on the first carbon atom adjacent to N are not hydroxyl groups and also provided that  $R^d$  and  $R^e$  on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group), and

$V$  is  $NR^8$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group).

23. The indole type thiazolidine compound and its salt according to Claim 22, wherein:

$R^1$  is  $-W-V-Z$ , wherein  $-W-V-$  is  $-CO-NR^8-$  ( $R^8$  is a hydrogen atom or a  $C_1-C_3$  alkyl group).

24. The indole type thiazolidine compound and its salt according to Claim 9, 10, 12, 20, 21 or 22, wherein:

$Y$  is  $-CH_2-$ ; and

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$R^4$  is a hydrogen atom.

25. The indole type thiazolidine compound and its salt according to Claim 9, 10, 12, 20, 21 or 22, wherein:

$Y$  is  $CHR^7$  ( $R^7$  forms a bond together with  $R^4$ ); and

5  $R^4$  forms a bond together with  $R^7$ .

26. A hypoglycemic agent containing the indole type thiazolidine compound or its salt according to Claim 1 as an active agent.

27. An aldose reductase inhibitor containing the indole 10 type thiazolidine compound or its salt according to Claim 1 as an active agent.

28. A pharmaceutical agent for preventing and treating diabetes mellitus and diabetic complications, which contains the indole type thiazolidine compound or its salt according to Claim 1 as an active agent.

**INTERNATIONAL SEARCH REPORT**

Internat'l Application No PCT/JP 96/00403	
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**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C07D417/06 C07D413/06 C07D417/14 A61K31/425 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- \*'&' document member of the same patent family

Date of the actual completion of the international search

13 May 1996

Date of mailing of the international search report

23.05.1996

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Authorized officer

Henry, J

## INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 96/00403

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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